^{188}Re-HDD/Lipiodol for Treatment of Hepatocellular Carcinoma: A Feasibility Study in Patients with Advanced Cirrhosis

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This study aimed to investigate the feasibility of the intraarterial administration of 3.7 GBq ^{188}Re-4-hexadecyl-1-2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol/lipiodol (^{188}Re-HDD/lipiodol) for treatment of hepatocellular carcinoma (HCC) in patients with moderately advanced cirrhosis. **Methods:** Patients with HCC and underlying cirrhosis classified as Child–Pugh B in terms of severity were eligible. Whole-body scintigraphies were performed at 4 time points after injection. Absorbed doses to the various organs were calculated according to the MIRD formalism. Urine was collected for 52 h after injection. Toxicity was assessed until 6 wk after administration by means of the Common Toxicity Criteria for Adverse Events (version 3.0) scale. Responses were evaluated on MRI and by α-fetoprotein (AFP) monitoring. **Results:** A mean activity ± SD of 3.7 ± 0.2 GBq ^{188}Re-HDD/lipiodol was administered in the hepatic artery to 12 patients; 36.2% ± 5.7% of the activity was excreted in the urine 52 h after injection. The absorbed dose to the liver, lungs, kidney, and thyroid was 7.6 ± 2.9, 4.8 ± 2.6, 0.8 ± 0.7, and 0.2 ± 0.1 Gy (mean ± SD), respectively. Two weeks after administration, 6 of 12 patients had adverse events consisting of aggravations of preexisting laboratory changes (3 patients), fatigue (2 patients), vomiting (1 patient), fever (1 patient), encephalopathy (1 patient), and ascites (1 patient). Toxicity assessment at week 6 revealed single cases of the worsening of hyperbilirubinemia, pleural effusion, thrombocytopenia, and dyspnea. Three patients dropped out of the study because of deterioration of their general condition. The response was assessable by MRI in 8 patients: 1 patient with a partial response and 7 patients with stable disease were reported. Nine patients with an initially elevated AFP were evaluated. Stable AFP was recorded in 1 patient and 3 showed a reduction, whereas a considerable increase was observed in 5 patients. **Conclusion:** After the administration of 3.7 GBq ^{188}Re-HDD/lipiodol, half of the Child–Pugh B patients in the present study had a worsening of their general condition or aggravation of preexisting symptoms. This was associated with a rise in AFP in a considerable number of patients. In the future, administration of the radiopharmaceutical as close to the tumor feeding arteries as possible might avoid further deterioration of the liver function and show enhanced antitumoral activity.

Key Words: hepatocellular carcinoma; radionuclide therapy; ^{188}Re; 4-hexadecyl-1-2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol; lipiodol

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Hepatocellular carcinoma (HCC) is a malignant epithelial tumor arising from parenchymatous liver cells (*1*). It is one of the world's most common malignancies, causing almost one million deaths annually (*2*). The major risk factor for HCC is cirrhosis. All types of cirrhosis predispose to HCC, but the incidence is particularly high in persistent infection with hepatitis B and hepatitis C and in alcoholic liver disease (*3*). Only a minority of patients presenting with HCC fulfill the eligibility criteria for curative surgery, either partial liver resection or liver transplantation. Local ablative therapies such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and transarterial chemoembolization (TACE) have proven to be useful in selected patients and are mainly applied to offer palliation or as bridging strategies in patients awaiting liver transplantation (*4,5*).

Lipiodol is a mixture of iodized ethyl esters of the fatty acids of poppyseed oil. Injection of lipiodol in the hepatic artery of HCC patients results in a selective and prolonged retention within the tumor. Although lipiodol alone does not appear to have any significant anticancer effect in hepatoma cells, radiolabeled lipiodol has proven to be toxic for hepatoma cells (*6*). To date lipiodol has been radiolabeled and clinically evaluated for the treatment of HCC with ^{131}I and ^{188}Re, respectively. Compared with ^{131}I, ^{188}Re presents several advantages for radionuclide therapy. ^{131}I has a long

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physical half-life of 8.03 d and emits a high energetic γ-ray of 364 keV, with an abundance of 82%, necessitating delayed hospitalization for radioprotection purposes. ^{188}Re emits a γ-ray of 155 keV at an abundance of 15%, which allows for imaging and limits radiation protection problems. The maximum β-energy of ^{131}I is only 606 keV, whereas, in ^{188}Re, β-particles are emitted with a maximal energy of 2.1 MeV. As a result, the maximum range of the high-energy ^{188}Re β-emission is about 3 times longer than that with ^{131}I (maximum range in water, 2.9 and 10 mm for ^{131}I and ^{188}Re, respectively) (*7*). Furthermore, the radionuclide is eluted from a ^{188}W/^{188}Re generator, which has a long useful shelf-life of several months and routinely provides a good yield of carrier-free ^{188}Re (*8*).

The first clinical results using ^{188}Re-4-hexadecyl-1-2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol/lipiodol (^{188}Re-HDD/lipiodol) were reported by Sundram et al. (*9,10*). The radiopharmaceutical was administered as close to the tumor feeding artery as possible and the administered activity was defined individually according to the findings after administration of a scout dose. Tolerance was excellent. In a pilot trial conducted by Lambert et al., a fixed activity of 3.6 GBq ^{188}Re-HDD/lipiodol was used and, in patients with well-compensated cirrhosis, further escalation of the activity seemed feasible (*11*). To our knowledge, no studies have been conducted to define the tolerance of ^{188}Re-HDD/lipiodol in patients having HCC with a moderately advanced underlying cirrhosis. The aim of the present study was to investigate the feasibility of ^{188}Re-HDD/lipiodol treatment for patients with a Child–Pugh B degree of liver cirrhosis. A secondary endpoint was response assessment.

MATERIALS AND METHODS

Synthesis and Quality Control of Radioconjugate

^{188}W/^{188}Re generators were purchased from the Oak Ridge National Laboratory and the Institut des Radio-Eléments (Fleurus, Belgium). Lyophilized kits containing the HDD chelator were provided by the Seoul National University Hospital and ^{188}Re-HDD/lipiodol was synthesized as described earlier (*12*). Briefly, the concentrated eluate (6 mL) from a commercially available ^{188}W/^{188}Re generator containing 11.1 GBq, was heated with the HDD/$SnCl_2$ kit at 100°C for 1 h to produce ^{188}Re-HDD complex (*13*). Three milliliters of lipiodol were added and mixed on a vortex to extract the ^{188}Re-HDD into the lipiodol. After centrifugation at 4,000*g*, the ^{188}Re-HDD/lipiodol fraction was separated. Finally, the ^{188}Re-HDD/lipiodol layer was washed with a 0.9% NaCl solution. Quality control was performed according to the method described by Jeong et al. by instant thin-layer chromatography (ITLC-SG plates, Gelman Sciences; mobile phase, 0.9% NaCl and acetone) (*14*). The total radiochemical yield was 50% ± 9% (mean ± SD). In all cases, radiochemical purity was >95%.

Patient Selection

The diagnosis of HCC was established by means of biopsy or conventional imaging techniques such as CT, MRI, and arteriography, eventually in conjunction with a serum α-fetoprotein (AFP) level of >400 ng/mL (*5*). For lesions of <2 cm, 2 radiologists had to reach a consensus on the diagnosis of HCC. The severity of the underlying cirrhosis was assessed by clinical examination and laboratory testing 1 wk before treatment. Only patients with a Child–Pugh B status according to the Child–Pugh scoring for cirrhosis were included in this study (Table 1) (*15*). The modified Child–Pugh classification system has been widely used in both alcoholic and nonalcoholic cirrhosis for assessment of severity of liver impairment and 1-y mortality based on the degree of ascites and encephalopathy, serum concentration of bilirubin, albumin, and prothrombin time. Child–Pugh grade A cirrhosis is considered as well-compensated disease, whereas a Child–Pugh B score reflects a significant functional compromise. Patients with Child–Pugh C cirrhosis have decompensated disease with a median survival of <1 y (*16*). Exclusion criteria were eligibility for liver resection, pregnancy and breast feeding, age <18 y, poor general condition (Karnofsky score <70%), white blood cell count <1,500/μL, and potentially toxic anticancer treatment in the preceding 6 wk. Contraindications for arteriography consisted of a serum creatinine level of >2 mg/dL, a prothrombin time of <50% of the normal value, or a platelet count of <50,000/μL. To comply with the radioprotective guidelines, inability to care for oneself and incontinence were additional contraindications. The study was approved by the institutional ethics committee and informed written consent was obtained from all patients.

Administration

Under local anesthesia, a 5-French diagnostic Cobra catheter was inserted transfemorally by the Seldinger technique. First, the portal vein was evaluated by catheterization of the superior mesenteric artery for performing mesentericoportography. Then, a diagnostic hepatic arteriogram was obtained by catheterization of the celiac trunk and common hepatic artery. Afterward, the diagnostic catheter or a microcatheter was introduced in the proper hepatic artery, and approximately 4 mL of ^{188}Re-HDD/lipiodol were injected slowly under fluoroscopic control. Whenever an aberrant arterial supply was present, the radioconjugate was injected selectively into the right and left hepatic artery separately. The volume of 4 mL was divided over the different hepatic arteries proportional to the volume of liver parenchyma supplied by the respective artery. To reduce uptake of free perrhenate in the thyroid or gastric mucosa, patients received 0.5 g sodium perchlorate orally before ^{188}Re-HDD/lipiodol administration followed by 1 g daily until discharge.

TABLE 1
Child–Pugh Classification

Parameter	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Ascites	No	Slight	Moderate
Encephalopathy	No	Grade I–II	Grade III–IV
Protrombin time (%)	>60	40–60	<40
INR	<1.7	1.7–2.3	>2.3

Five to 6 points is scored as Child–Pugh A cirrhosis, 7–9 points is scored as Child–Pugh B cirrhosis, and 10–15 points is scored as Child–Pugh C cirrhosis.

INR = International Normalized Ratio.

Pharmacokinetic and Dosimetric Study

After ^{188}Re-HDD/lipiodol administration, patients were hospitalized in a dedicated radionuclide therapy room for 3–4 d. Four whole-body scintigraphies were acquired at 2.1 ± 1.7, 22.7 ± 1.2, 28.9 ± 2.1, and 60.1 ± 8.2 h (mean ± SD) after administration, using a double-head (AXIS) or triple head (IRIX) γ-camera (Philips) equipped with medium-energy, parallel-hole collimators. The imaging window was set at 155 keV ± 20%. Scan speed varied from 30 to 10 cm/min depending on the time elapsed since administration. Regions of interests (ROIs) were drawn around the total body, the liver (including tumor), the lungs, a background region, and a syringe containing a known activity of ^{188}Re (mean activity ± SD, 16.0 ± 1.9 MBq). The background-corrected geometric mean of the total counts in the ROIs was used to calculate the total amount of activity in these regions, using the known activity in the syringe and experimental factors determined on an antropomorphic phantom (Alderson Heart/Thorax SPECT phantom) for the conversion of the syringe activity into organ activity (Fig. 1). In the latter conversion factors, the attenuation and scatter effects in this standard phantom were considered. The overall uncertainty using this methodology for the activity calculation was <18%. Monoexponential time–activity curves were generated for the total body, the liver, and the lungs using SPSS 10.0 software, and source organ residence times were determined. Absorbed doses to the various organs were calculated according to the MIRD formalism (*17*).

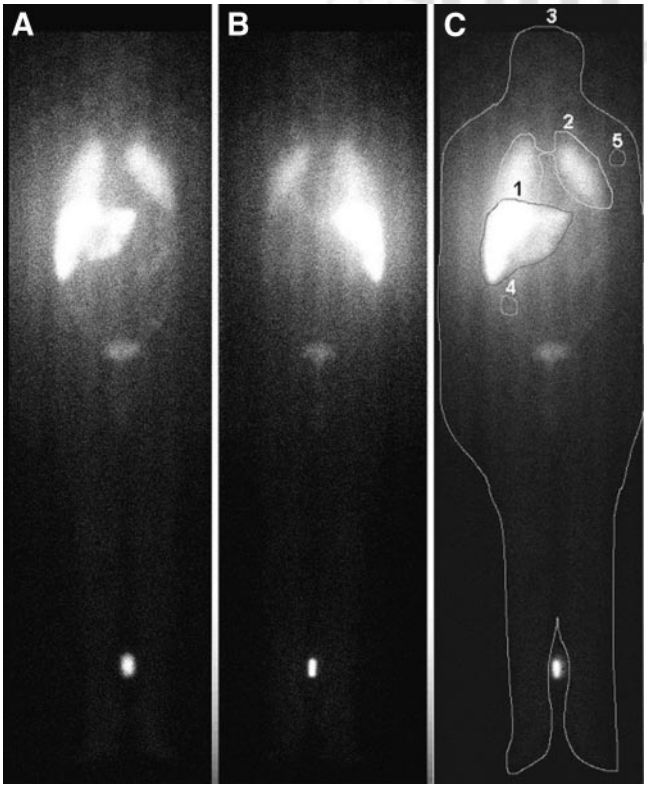

FIGURE 1. Anterior (A) and posterior (B) view of whole- body scintigraphy (patient 12) 28 h after administration of 3.7 GBq ^{188}Re-HDD/lipiodol. (C) Illustration of ROI definitions on geometric mean combination of posterior and anterior view: liver (1), lungs (2), whole body (3), background to liver (4), background to lungs (5).

Urine was collected for 52 h and samples were analyzed in a NaI(Tl) 3″ × 3″ γ-well counter calibrated for ^{188}Re (Cobra II; Perkin Elmer).

The patient's dose rate was regularly measured at 1-m distance of the liver region using a survey meter.

Toxicity and Response Assessment

Laboratory testing of red and white blood cells and platelets, liver function, renal function, and serum AFP were performed 1 wk before treatment, at discharge, and 2 and 6 wk after injection. Laboratory findings were compared by means of Friedman statistical testing and the significance level was set at $P < 0.05$ (SPSS, version 10.0). Clinical evaluation of toxicity was performed daily during hospitalization and 2 and 6 wk later. Toxicity was scored by means of the common toxicity criteria (Common Toxicity Criteria for Adverse Events, version 3.0; Cancer Therapy Evaluation Program). Radiologic response was assessed by means of the response evaluation criteria in solid tumors (RECIST) on MR images acquired 6 wk after treatment (*18*). Patients without evidence of progressive disease were eligible for repetitive treatment sessions with a 12-wk interval.

RESULTS

Twelve patients underwent a single treatment session. The administered activity per session was 3.7 ± 0.2 GBq (mean ± SD). Patient characteristics are summarized in Table 2. The mean age was 63 y and the sex ratio was 9 males versus 3 females. Four patients presented with portal vein thrombosis (PVT) on arteriography. Okuda score and Cancer of the Liver Italian Program (CLIP) score are prognostic staging systems for HCC. Prognosis worsens with increasing scores (*19,20*).

Pharmacokinetic and Dosimetric Study

Urinary excretion was measured in all patients and 36.2% ± 5.7% (mean ± SD) of the administered activity was excreted within 52 h after injection. Because of technical problems, datasets for calculation of the absorbed doses to the organs were complete in 6 of 12 patients (Table 3). Effective half-lives for whole body, liver, and lungs were 15.1 ± 1.2 h, 16.2 ± 0.3 h, and 16.4 ± 0.2 h (mean ± SD), respectively. In all patients, the dose rate at 1 m dropped below 20 μSv/h within the first 24 h after administration and did not exceed 5 μSv/h on day 2.

Toxicity

Table 4 summarizes the adverse events according to the Common Toxicity Criteria, version 3.0. Only the events reflecting a worsening compared with the baseline values are tabulated. Four patients dropped out for response assessment 6 wk after treatment: Patient 2 received a liver transplantation at week 5 and patients 5, 7, and 10 did not attend follow-up visits at week 6 because of a worsening of their general condition. Seven patients experienced a severe adverse event, consisting of a grade 3 or 4 event. In 3 patients, this event was associated with a rising level of tumor marker and, thus, the relation to the radiopharmaceutical remains unclear. Two patients had a severe aggravation of their

TABLE 2
Patient Characteristics

Patient no.	Age (y)	Sex	Risk factor*	Child–Pugh score	Okuda score (I–III)	CLIP score (0–6)	PVT	Previous treatment† (interval in wk)
1‡	70	M	HCV	B9	II	2	No	None
2‡	71	M	ALC	B9	II	3	No	^{131}I (16)
3	60	M	None	B7	I	2	No	Chemotherapy IV (22)
4	61	F	HCV	B9	II	3	No	Resection (56)
5	48	M	ALC	B7	I	3	No	Tamoxifen
6	77	M	None	B7	II	2	Yes	None
7	75	M	ALC	B8	II	3	Yes	None
8	59	F	HCV	B7	II	2	No	None
9	54	M	HC, ALC	B9	II	4	Yes	None
10	68	F	ALC	B7	I	4	Yes	^{131}I (12)
11	44	M	HCV	B7	II	2	No	TACE (22)
12‡	72	M	HCV	B7	I	1	No	^{188}Re (18)

*Risk factors: HCV = chronic hepatitis C infection; ALC = alcohol; HC = hemochromatosis.
†Recent previous treatment: radionuclide therapy by means of ^{131}I-lipiodol (^{131}I) or ^{188}Re-HDD/lipiodol (^{188}Re); IV = intravenous.
‡Patients included in initial phase I study (*11*).
CLIP = Cancer of the Liver Italian Program; PVT = portal vein thrombosis.

jaundice. Patient 10 developed rapidly progressive ascites at week 2. She could not attend further follow-up visits and died 8 wk after treatment. Patient 12 had mild dyspnea and coughing after his first treatment with ^{188}Re-HDD/lipiodol, which was performed in the framework of a phase I pilot trial conducted earlier at our institution. After 18 wk, his level of tumor marker was rising and his cirrhosis had worsened to a Child–Pugh B degree, whereas he presented initially with a Child–Pugh A cirrhosis. A second treatment was performed in the framework of the present study and his pulmonary symptoms reoccurred. A complete relief of the symptoms was achieved with oral steroid treatment. However, the patient discontinued the medication and relapsed.

The most common adverse event during hospitalization consisted of a rise in the level of aminotransferase (AST) or alanine aminotransferase (ALT). The early onset of this phenomenon suggests a relation with the radionuclide administration. However, Friedman statistical testing over the various time points did not reach the level of significance ($P < 0.05$) for any of the tested parameters (ALT, AST, γ-glutamyl transferase, red blood cells, white blood cells, platelets, prothrombin time, albumin, total bilirubin, and creatinine). Values for white blood cells, platelets, bilirubin, ALT, and AST at baseline, discharge, week 2, and week 6 are depicted in Figure 2.

TABLE 3
Mean Absorbed Dose Estimations of 6 Patients After Treatment with 3.6 ± 0.2 GBq ^{188}Re-HDD/Lipiodol

Target organ	Absorbed dose (Gy)	
	Mean ± SD	Range
Liver	7.6 ± 2.9	4.6–11.8
Lungs	4.8 ± 2.6	1.7–10.4
ULI wall	0.6 ± 0.4	0.2–1.4
Kidneys	0.8 ± 0.7	0.2–1.6
Stomach	0.3 ± 0.1	0.1–0.4
LLI wall	0.3 ± 0.1	0.1–0.4
Thyroid	0.2 ± 0.1	0.1–0.4
Red marrow	0.3 ± 0.1	0.1–0.4
Whole body	0.6 ± 0.1	0.5–0.7

ULI = upper large intestine; LLI = lower large intestines.

Response

Response on MRI. Four patients dropped out for response assessment. One patient (patient 8) presented with 2 small tumors measuring 1.9 and 1.8 cm on MRI. On arteriography, hypervascular blushes were obvious but a CT scan 2 wk after lipiodol administration failed to show prolonged uptake of lipiodol in the lesions. In this patient, a partial response was obtained with no evidence of HCC lesions on subsequent imaging. The AFP level dropped from 45 to 26 ng/mL. This patient underwent a liver transplantation 12 wk after radionuclide therapy and no neoplastic lesions were found in the explant liver. The remaining 7 patients had stable disease.

Response on AFP. Changes in tumor marker are listed in Table 4. In 9 patients, AFP levels were elevated before treatment. In 3 of 9 treatment sessions, a reduction in tumor marker (range, 23%–63%) was recorded 6 wk later, but this was not observed in patients with baseline AFP levels exceeding 400 ng/mL. Five patients showed a considerable rise in their tumor marker at follow-up visits 2 or 6 wk after therapy.

DISCUSSION

Available literature concerning radionuclide therapy for HCC comprises reports of mixed patient populations of

TABLE 4
Adverse Events and Changes in AFP Level

Patient no.	Adverse event	Grade before → after therapy	Attribution to investigational agent	Change in AFP
1	None			NA
2	Fatigue (day 2)	0 → 2	Possibly	+30% (week 2); dropout (week 5: transplanted)
	Increase in bilirubin (week 2)	3 → 4	Possibly	
	Increase in AST (day 2–week 2)	1 → 2	Possibly	
3	Fever (day 2–3)	0 → 1	Probably	NA
	Fatigue (week 2)	1 → 2	Possibly	
	Increase in bilirubin (week 2)	2 → 3	Possibly	
	Increase in bilirubin (week 6)	2 → 4	Possibly	
4	Vomiting (day 0)	0 → 1	Probably	+68% (week 6)
	Fever (day 0)	0 → 1	Probably	
	AST elevation (day 2)	2 → 3	Probably	
	Hypoalbuminemia (day 2–week 2)	1 → 2	Possibly	
	Ascites (week 6)	0 → 1	Possibly	
5	AST elevation (day 2–week 2)	3 → 4	Possibly	NA dropout (week 6: worsening general condition)
6	None			+69% (week 6)
7	Encephalopathy (day 1)	0 → 2	Possibly	+25% (week 2); dropout (week 6: liver failure)
8	Pleural effusion (week 6)	2 → 3	Unlikely	−43% (week 6)
9	ALT elevation (day 2–week 6)	1 → 2	Possibly	+37% (week 6)
	AST elevation (day 2)	1 → 3	Possibly	
	AST elevation (week 2–week 6)	1 → 2	Possibly	
	Increase in bilirubin (week 2)	1 → 2	Possibly	
10	Ascites (week 2)	0 → 3	Possibly	Stable (week 2); dropout (week 6: liver failure)
11	Increase in bilirubin (week 6)	1 → 2	Possibly	−63% (week 6)
12	Leukopenia (week 2–week 6)	0 → 1	Probably	−23% (week 6)
	Thrombocytopenia (week 6)	1 → 3	Probably	
	Cough, dyspnea, pulmonary fibrosis (week 6)	1 → 2	Possibly	
	Reduced carbon monoxide diffusion capacity	2 → 3	Possibly	

NA = not applicable; AST = aminotransferase; ALT = alanine aminotransferase.

mainly Child–Pugh A and B patients and does not allow for conclusions focusing on Child–Pugh B patients in particular (*9,10,21,22*). Available data concerning other locoregional treatment strategies for HCC as well are limited to patients with well-compensated liver cirrhosis. In a meta-analysis conducted by Llovet and Bruix, TACE with cisplatin or doxorubicin was reported to improve the 2-y survival (*23*). This publication confirmed TACE in its role of standard treatment for inoperable HCC. However, the randomized controlled trials considered in this meta-analysis consisted of 70%–100% Child–Pugh class A patients. Hence, its conclusions should be interpreted with caution if patients with advanced underlying liver dysfunction are considered. The best results were obtained in patients who underwent repeated TACE. Llovet and Bruix suggested that repeated treatment sessions are often feasible only in patients with well-preserved liver function, in whom the antitumoral effects are not offset by its toxic effects on the liver parenchyma. Although the present study design allowed for repeated ^{188}Re-HDD/lipiodol administrations with 12-wk intervals, most of the patients were not eligible for repeated treatment because of a worsening of their general condition. These findings probably reflect a poor tolerance or lack of antitumoral effect in this patient group.

Sundram et al. reported 2 cases of pleural effusion and these were attributed to radiation-induced pneumonitis (*10*). In our study, grade 3 lung toxicity developed in patient 12. The absorbed cumulative lung dose was estimated to be 10.4 Gy—hence, too low to explain this evolution. The timing of the occurrence of his symptoms and the associated bone marrow depression are suggestive for an increased sensitivity to ionizing radiation in this patient (*11*). Although a causal relationship is not clear, it is recommended that patients with pulmonary complaints after ^{188}Re-HDD/lipiodol therapy should not be eligible for repeated treatment sessions. Other adverse events in this series were related to underlying liver dysfunction and, considering the features of this specific patient population, it is difficult to assess the cause of these adverse events: progressive underlying cirrhosis, tumor growth, as well as toxicity due to the

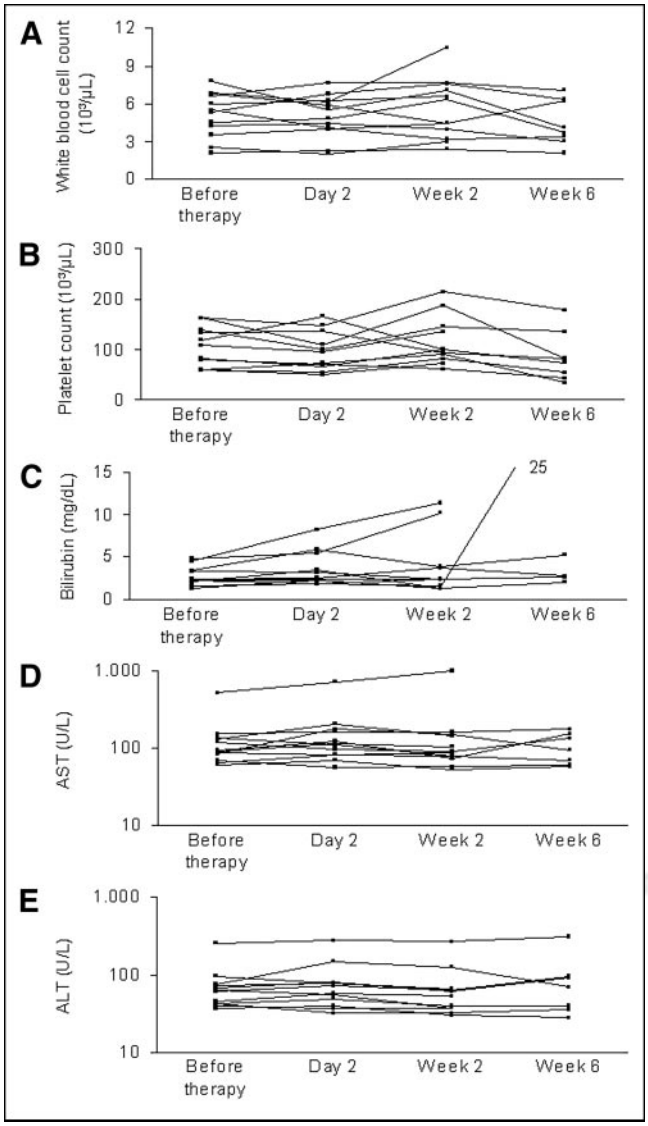

FIGURE 2. Changes in white blood cells (A), platelets (B), bilirubin (C), AST (D), and ALT (E) over time.

treatment may explain further liver decompensation. Even in patients with a rise in the AFP level, factors other than tumor progression might explain the occurrence of adverse events. A transient increase in AFP was documented after radiotherapy for HCC by Zeng et al. (*24*) and was thought to reflect tumor repopulation. On the other hand, liver regeneration is a well-known cause of an unspecific rise in AFP (*24*).

Urinary excretion in the present study was comparable with earlier findings in a group of patients with well-compensated cirrhosis. ITLC analysis showed that the activity in the urinary samples was perrhenate (*11*). The absorbed doses to liver, lungs, and thyroid were compared with the dose estimates obtained in a group of 14 Child–Pugh A patients treated with the same activity at our institution. No significant difference in dose estimates between Child–Pugh A and B patients was found (Mann–Whitney statistical test, SPSS version 10.0; $P < 0.05$) and, hence, it is unlikely that the occurrence of adverse events was related to a different distribution or elimination in Child–Pugh B patients.

In contrast to the initial experiences of patients with well-preserved liver function, the present findings of patients with moderately advanced cirrhosis do not support further evaluation of administration of 3.7 GBq ^{188}Re-HDD/lipiodol in the proper hepatic artery or both left and right branch. A hyperselective approach, consisting of injecting the radiopharmaceutical as close to the tumor feeding artery as possible, might avoid further liver decompensation and induce an enhanced antitumoral effect. As the case for local ablative techniques such as PEI and RFA, development of HCC lesions in untreated segments remains a risk in such a strategy (*23*). Therefore, part of the activity could be given in the proper hepatic artery and the rest of the activity could be administered using as hyperselective approach as possible. Future research should elucidate whether modified administration protocols yield better results.

CONCLUSION

After administration of 3.7 GBq ^{188}Re-HDD/lipiodol in 12 patients with moderately advanced cirrhosis, 36.2% ± 5.7% of the injected activity was renally excreted within 52 h after injection. The absorbed dose (mean ± SD) to the liver, lungs, kidney, and thyroid was 7.6 ± 2.9, 4.8 ± 2.6, 0.8 ± 0.7, and 0.2 ± 0.1 Gy, respectively.

Treatment was well tolerated in 5 of 12 patients. Seven patients had a worsening of their general condition, an aggravation of preexisting symptoms, or severe laboratory abnormalities. This was associated with a rise in the AFP level in a considerable number of patients. The results of the present feasibility study do not support further evaluation of the administration of 3.7 GBq ^{188}Re-HDD/lipiodol in the proper hepatic artery or both right and left hepatic artery. In the future, administration of the radiopharmaceutical as close to the tumor feeding arteries as possible might avoid further deterioration of the liver function and show enhanced antitumoral activity.

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