Biologic Dosimetry of ^{188}Re-HDD/Lipiodol Versus ^{131}I-Lipiodol Therapy in Patients with Hepatocellular Carcinoma

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One approach to treatment of primary hepatocellular carcinoma (HCC) is intraarterial injection of ^{131}I-lipiodol. Although clinical results have been positive, the therapy can be improved by using ^{188}Re instead of ^{131}I as the radionuclide. ^{188}Re is a high-energy β-emitter, has a shorter half-life than ^{131}I, and has only low-intensity γ-rays in its decay. The present study compared the cytotoxic effect of the radionuclide therapy in HCC patients treated with ^{131}I-lipiodol and ^{188}Re-4-hexadecyl 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD)/lipiodol. To this end, dicentric chromosomes (DCs) were scored in metaphase spreads of peripheral blood cultures. The equivalent total-body dose was deduced from the DC yields using an in vitro dose–response curve. **Methods:** Twenty ^{131}I-lipiodol treatments and 11 ^{188}Re-HDD/lipiodol treatments were performed on, respectively, 16 and 7 patients with inoperable HCC. Patients received a mean activity of 1.89 GBq of ^{131}I-lipiodol or 3.56 GBq of ^{188}Re-HDD/lipiodol into the liver artery by catheterization. For each patient, a blood sample was taken during the week before therapy. A blood sample was also taken 7 and 14 d after administration for the patients treated with ^{131}I-lipiodol and 1 or 2 d after administration for the patients treated with ^{188}Re-HDD/lipiodol. **Results:** The mean DC yield of ^{188}Re-HDD/lipiodol therapy (0.087 DCs per cell) was significantly lower than that of ^{131}I-lipiodol therapy (0.144 DCs per cell) for the administered activities. Corresponding equivalent total-body doses were 1.04 Gy for ^{188}Re-HDD/lipiodol and 1.46 Gy for ^{131}I-lipiodol. Data analysis showed that, in comparison with ^{131}I-lipidol, ^{188}Re-HDD/lipiodol yielded a smaller cytotoxic effect and a lower radiation exposure for an expected higher tumor-killing effect. **Conclusion:** ^{188}Re is a valuable alternative for ^{131}I in the treatment of HCC with radiolabeled lipiodol, and a dose escalation study for ^{188}Re-HDD/lipiodol therapy is warranted.

Key Words: ^{131}I-lipiodol therapy; ^{188}Re-HDD/lipiodol therapy; biologic dosimetry; dicentric chromosome assay

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Primary hepatocellular carcinoma (HCC) is the most common primary liver malignancy and among the 10 most common tumors in the world. Chronic infection with the hepatitis B or C virus appears to be the most important risk factor for HCC. Patients with HCC have a poor prognosis, with a 5-y survival rate of less than 5%. Survival chances are best when liver transplantation or surgical resection is possible, but these therapies are applicable to only a few patients. For most patients, only palliative options remain. These include percutaneous ablation therapy (local) and intraarterial chemotherapy with or without subsequent embolization (locoregional) (*1*).

Metabolic radiation therapy using arterial administration of ^{131}I-lipiodol has shown effective clinical results and good tolerance by patients. For patients with portal vein thrombosis, ^{131}I-lipiodol has proven to be effective, and among patients treated surgically, ^{131}I-lipiodol is the only auxiliary treatment proven effective at reducing recurrence (*2*,*3*). The treatment can also be used in a curative setting, with ^{131}I-lipiodol being given neoadjuvantly before liver transplantation (*4*).

Despite the encouraging results obtained with ^{131}I-lipiodol, the therapy—and especially the radionuclide—has important limitations. ^{131}I is characterized by a high γ-ray emission (365 keV, 81%), which allows the imaging but is, together with the 8-d physical half-life of ^{131}I, also responsible for long hospitalizations and limitation of the administered activity (*5*). On the other hand, the maximal β-energy of ^{131}I is only 606 keV (89%) (*6*), allowing only rather small tumors to be irradiated efficiently. Because of the high-energy γ-radiation of ^{131}I, distant tumor locations can still be irradiated by the cross-fire effect. However, Monte Carlo simulations show that the contribution of this cross-fire effect is only 10% in large tumors. ^{188}Re has several physical characteristics that favor its replacing ^{131}I in palliative therapy. The radionuclide has a relatively short physical half-life of 17 h and a maximal β-energy of 2.1 MeV (72%), with a 15% γ-component of 155 keV in its decay

(*6*). The high-energy ^{188}Re β-emission can destroy cells in a radius of several millimeters, and the 155-keV γ-rays allow γ-camera imaging. Furthermore, ^{188}Re is eluted from a ^{188}W/^{188}Re generator, which has a long useful shelf-life of several months and provides a good yield of carrier-free ^{188}Re routinely (*7*). ^{188}Re is coupled indirectly to lipiodol using 4-hexadecyl 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD) as a chelating agent (*8*). Recently, promising clinical results were published for an International Atomic Energy Agency multicenter study using ^{188}Re-HDD/lipiodol (*9*). However, ^{131}I-lipiodol and ^{188}Re-HDD/lipiodol were not compared.

Cytogenetic tests play an important role in the detection of biologic effects in patients exposed to ionizing radiation. Chromosomal aberrations, especially dicentric chromosomes (DCs), induced by ionizing radiation in human lymphocytes can be used as indicators of radiation exposure. Biologic dosimetry based on the analysis of DCs has been used since the mid 1960s. The aberrations scored in lymphocytes can be interpreted in terms of absorbed dose by reference to a dose–response calibration curve (*10*).

To compare the cytotoxic effect of ^{188}Re-HDD/lipiodol radionuclide therapy with that of ^{131}I-lipiodol therapy in the framework of a phase I study, we studied the frequency of DCs in a cohort of HCC patients given ^{188}Re or ^{131}I therapy. The equivalent total-body dose (ETBD) was estimated using an in vitro dose–response curve.

MATERIALS AND METHODS

^{188}Re-HDD/Lipiodol Preparation

The HDD lyophilized kits were obtained from Seoul National University Hospital (*8*). Briefly, the concentrated eluate from the ^{188}W/^{188}Re generator is heated with HDD/$SnCl_2$ in a boiling water bath for 1 h to produce ^{188}Re-HDD complex. Lipiodol is then added, stirred in a vortex mixer, and centrifuged to extract the ^{188}Re-HDD into the lipiodol. The ^{188}Re-HDD/lipiodol radioconjugate is stable for at least 4 h (radiochemical purity > 95%).

Study Population

Between February 2002 and July 2003, 20 ^{131}I-lipiodol treatments (IL group, $n = 20$), and 11 ^{188}Re-HDD/lipiodol treatments (ReL group, $n = 11$) were administered in the Ghent University Hospital to, respectively, 16 and 7 patients with inoperable HCC. The patients in the IL group and in the ReL group were admitted the day before treatment and the day of treatment, respectively, for intravenous prehydration and initiation of thyroid blocking with either potassium iodide capsules (100 mg/d for 2 wk, IL group) or sodium perchlorate drops (500 mg for 5 d, ReL group). The patients received an activity of 1.89 GBq (SD, 0.15) of ^{131}I-lipiodol (Lipiocis; Schering CIS BIO International) or 3.56 GBq (SD, 0.17) of ^{188}Re-HDD/lipiodol into the liver artery by catheterization. The ^{131}I-lipiodol and ^{188}Re-HDD/lipiodol treatment programs were approved by the Ethical Committee of our hospital. Fifteen patients of the IL group and 4 patients of the ReL group received a single treatment. In each group, 2 patients received 2 consecutive treatments and 1 patient received 3 consecutive treatments over about half a year. An overview of the data is given in Table 1.

Sample Collection

From each patient in the study, a heparinized blood sample was taken during the week before therapy. From each patient treated with ^{131}I-lipiodol, a blood sample was obtained 7 and 14 d after administration. Taking into account the shorter half-life of ^{188}Re, a blood sample from each patient treated with this radionuclide was obtained 1 d (21 h; SD, 3) and 2 d (51 h; SD, 2) after administration.

Lymphocyte Culture

From each sample, 2 blood cultures were made by the addition of 0.5 mL of whole blood to 4.5 mL of RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum, 1% antibiotics (penicillin and streptomycin), and 1% L-glutamine. The lymphocytes were stimulated to divide with 1% phytohemagglutinin. The cultures were incubated at 37°C for 48 h. Three hours before arrest of the cultures, Colcemid (0.2 μg/mL; Alexis Biochemicals) was added to block the cells at metaphase. The cells were harvested by centrifugation of the samples, and the cell pellets were resuspended in 0.075 mol/L KCl for 15 min at 37°C. After the hypotonic shock, the cells were fixed 3 times in cold methanol:acetic acid (3:1). Finally, cells were dropped on clean slides and stained with 6% Romanovsky's Giemsa solution. Three hundred well-spread metaphases were analyzed for the presence of DCs.

ETBD

The ETBD is the absorbed dose of ionizing radiation, which, if received homogeneously by the whole body, would produce the same yield of DCs as observed in the patients. The ETBD was derived from the increase of the DC yield in the blood samples of each patient, 1 and 2 wk (^{131}I) or 1 and 2 d (^{188}Re) after administration of the activity. The ETBD was calculated from an in vitro dose–response curve, $Y = \alpha D + \beta D^2$, with Y the DC yield observed and D the dose. To determine the in vitro dose–response curve, blood samples of 10 HCC patients were, before phytohemagglutinin stimulation, irradiated in a 37°C water bath with ^{60}Co γ-rays with doses of 0.5, 1, 2, and 3 Gy at 1 Gy/min or sham irradiated.

Total-Body Scintigraphy and MIRD Dosimetry

For each patient, a set of biplanar anteroposterior total-body scintigraphic images was recorded after the therapy. The IL patients and the ReL patients received, respectively, 2 (7 and 14 d after therapy) and 4 (22, 30, 54, and 76 h after therapy) posttherapy scans. A syringe containing a known activity of ^{131}I or ^{188}Re in a polymethylmethacrylate phantom was scanned along with the patient. All scans were obtained with a IRIX camera (Philips) fitted with high-energy and medium-energy parallel-hole collimators for the IL and ReL patients, respectively.

For 6 of the 20 ^{131}I-lipiodol treatments and 2 of the 11 ^{188}Re-HDD/lipiodol treatments, a complete set of posttherapy scintigraphy scans was not available. Hence, the total-body dose could be calculated for only 14 ^{131}I-lipiodol and 9 ^{188}Re-HDD/lipiodol treatments.

On the HERMES system (Nuclear Diagnostics), irregular regions of interest were drawn around the syringe, the total body, the liver (including tumor), the lungs, and a background region on the

TABLE 1
Overview of the Demographic Data and Results

Patient no.*	Age (y)†	Sex	Etiology	Stage	Administered activity (GBq)	Dicentrics/cell		
						Pre	Post1	Post2
IL1	51	F	HCV	Child A/B	1.93	0.000	0.073	—
IL2a	63	M	Ethanol	Child A	1.90	0.020	0.065	0.130
IL2b	63	M	Ethanol	Child A	2.09	0.003	0.087	0.130
IL3a	64	M	HCV + HBC	Child A	1.77	0.000	0.020	0.060
IL3b	64	M	HCV + HBC	Child A	1.73	0.013	0.037	0.073
IL4a	54	M	HeCh + ethanol	Child A	1.92	0.007	0.083	0.140
IL4b	54	M	HeCh + ethanol	Child A	1.64	0.082	0.183	0.233
IL4c	54	M	HeCh + ethanol	Child A	1.95	0.157	0.270	0.357
IL5	57	M	Ethanol	Child A	2.02	0.000	0.050	—
IL6	71	M	HCV + ethanol	Child B	2.02	0.010	—	0.267
IL7	60	M	HBV	Child B	1.97	0.000	0.020	—
IL8	55	M	HCV	Child A	2.05	0.010	0.093	—
IL9	64	F	HCV	Child A	2.05	0.000	0.060	0.083
IL10	61	M	HCV	Child A	1.79	0.000	0.123	0.127
IL11	72	F	HCV	Child A	1.88	0.000	0.230	0.247
IL12	53	F	HCV	Child B	1.95	0.003	0.027	—
IL13	24	F	—	Fibrolamellar	1.84	0.007	0.030	0.045
IL14	59	F	HCV	Child A	1.45	0.007	0.062	—
IL15	63	M	HCV	Child A	1.88	0.000	0.267	0.267
IL16	87	M	Ethanol	Child A	1.99	0.003	0.143	0.157
Mean					1.89	0.016	0.101	0.165
SD					0.16	0.038	0.081	0.094
ReL1a	71	F	HCV	Child A	3.73	0.191	0.257	0.310
ReL1b	71	F	HCV	Child A	3.72	0.267	0.335	0.302
ReL1c	71	F	HCV	Child A	3.27	0.243	0.304	0.373
ReL2	70	M	HCV + ethanol	Child B	3.48	0.067	0.122	0.159
ReL3	70	M	Ethanol	Child B	3.41	0.000	0.020	0.043
ReL4	68	M	HCV	Child B	3.74	0.013	0.050	0.060
ReL5	60	F	HCV	Child A	3.58	0.000	0.100	0.150
ReL6a	71	M	HCV	Child A	3.71	0.000	0.123	0.120
ReL6b	72	M	HCV	Child A	3.66	0.100	0.180	0.194
ReL7a	75	M	HeCh	Child A	3.54	0.000	0.037	0.050
ReL7b	75	M	HeCh	Child A	3.35	0.080	0.143	0.157
Mean					3.56	0.087	0.152	0.174
SD					0.17	0.102	0.107	0.111

*The final letter (a–c) indicates different therapies for the same patient.

†At time of treatment.

Pre = before administration of the radionuclide; Post1 = 7 d (^{131}I-lipiodol) or 1 d (^{188}Re-HDD/lipiodol) after administration of the radionuclide; Post2 = 14 d (^{131}I-lipiodol) or 2 d (^{188}Re-HDD/lipiodol) after administration of the radionuclide; HCV = hepatitis C virus; HBV = hepatitis B virus; HeCh = hemochromatosis.

first scan. The regions of interest were mirrored to the posterior image and copied to each subsequent scan. The background-corrected geometric mean of the total counts in the regions of interest was used to calculate the total amount of activity in the total body, the liver, and the lungs, using the known activity in the syringe. Then, the cumulative activity of the total body, the liver, and the lungs was calculated from the area under the time–activity curve and was represented by a single exponential fit drawn through the data points of all consecutive total-body scintigraphy scans. Absorbed doses to the total body, the liver, and the lungs were calculated according to the MIRD formula, using the MIRD-DOSE3.0 software package (Oak Ridge Associated Universities) (*11*). Because of the heterogeneous dose distribution in the body and the inhomogeneous distribution of blood throughout the body (10% in the liver; 6% in the lungs) (*12*), the total-body absorbed dose cannot be used as a physical estimate of biologic ETBD. Therefore, the absorbed dose to the blood was calculated as the weighted sum of the doses to the liver, lungs, and remainder of the body, with the percentage of the blood pool in these compartments as a weighted factor.

An example of total-body scans for ^{131}I-lipiodol and ^{188}Re-HDD/lipiodol therapy for the same patient is given in Figure 1. The ^{188}Re-HDD/lipiodol therapy was administered several months after the ^{131}I-lipiodol therapy.

Statistical Analysis

Linear-quadratic best fits were calculated using SPSS 10.0 software (SPSS Inc.). Statistical analysis was performed using MedCalc, version 4.0 (http://medcalc.med-ia.net/). Differences between 2 populations were investigated using a 2-tailed Mann–

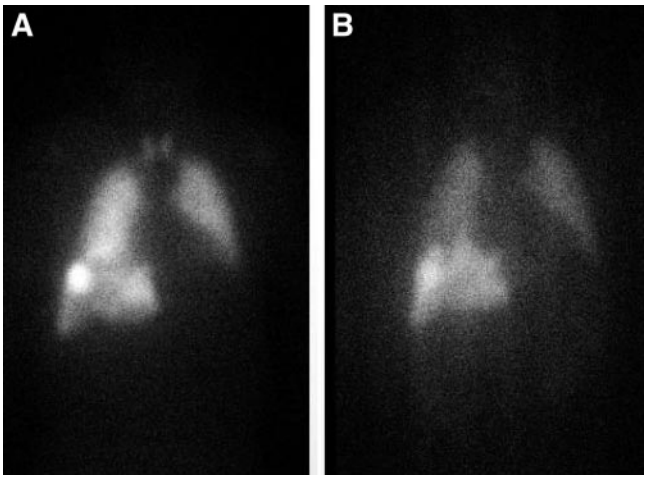

FIGURE 1. Total-body scans for ^{131}I-lipiodol (A) and ^{188}Re-HDD/lipiodol (B) for the same patient. These scans were obtained 14 d and 54 h, respectively, after administration of the activity.

Whitney test. The χ^2 test was used to compare the proportion of radiosensitive individuals in the patient and control populations.

RESULTS

In Vitro Dose Response

Figure 2 compares the in vitro induced DC yields for the HCC patients and the standard in vitro dose–response curve for a healthy population. Most HCC patients showed, for the entire studied dose range, more DCs per cell than did the healthy controls. At the 2-Gy dose, the differences between the HCC patients and the controls were statistically significant ($P = 0.023$, Mann–Whitney). When the 90th percentile of the healthy-control distribution was used as a cutoff, 60% of the HCC patients had elevated values of DCs at 2 Gy of in vitro irradiation ($P = 0.06$, χ^2; Fig. 3).

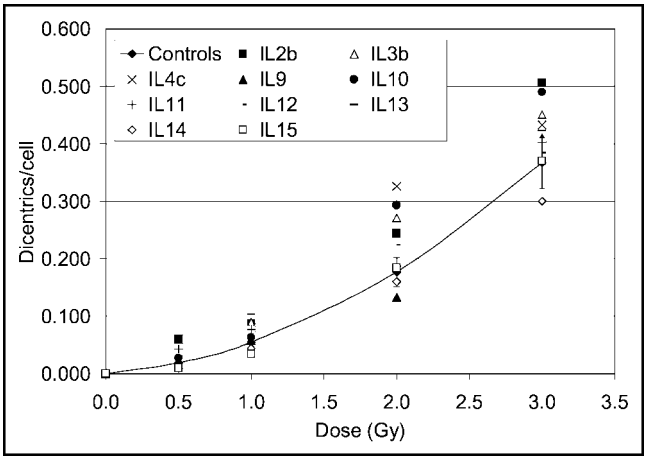

FIGURE 2. Yield of DCs in lymphocytes of HCC patients after in vitro irradiation, vs. the standard dose–response curve for a healthy population.

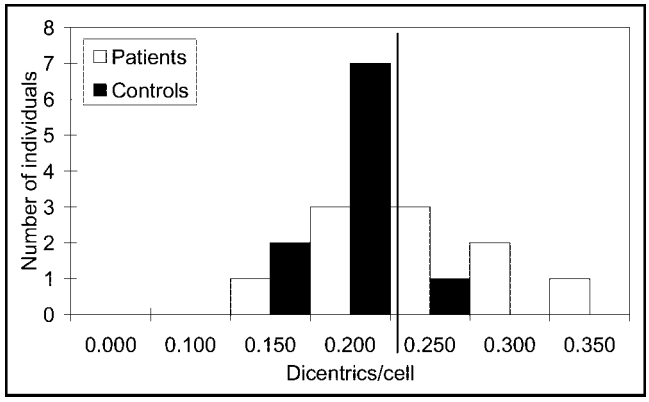

FIGURE 3. Distribution of radiation-induced DCs after 2 Gy of in vitro irradiation in healthy donors and HCC patients. The vertical line represents the cutoff between radiosensitive and nonradiosensitive individuals based on the 90th percentile of the control population.

DCs: ^{188}Re-HDD/Lipiodol Versus ^{131}I-Lipiodol Therapy

An overview of the results is given in Table 1. Missing values are due to failure of the cell culture, severe health problems in patients, or patients who left the study protocol. The mean DC yield, after background correction, observed in patients treated with ^{131}I-lipidol was 0.085 DCs per cell (SD, 0.068) 1 wk after therapy, compared with 0.065 DCs per cell (SD, 0.029) after 1 d in patients treated with ^{188}Re-HDD/lipiodol. Statistical significance ($P = 0.038$, Mann–Whitney) between the ^{131}I and the ^{188}Re groups was reached at the second time point: 0.144 DCs per cell (SD, 0.075) for ^{131}I-lipiodol after 2 wk and 0.087 DCs per cell (SD, 0.040) for ^{188}Re-HDD/lipiodol after 2 d.

Three patients of the IL group and 3 of the ReL group received multiple subsequent treatments. The DC yield before therapy, 1 and 2 wk after therapy for ^{131}I, and 1 and 2 d after therapy for ^{188}Re are plotted against time in Figure 4. The figure shows that the increase in DC yield 2 wk (^{131}I) or 2 d (^{188}Re) after administration of the therapeutic activity at least partially recovered by the time of the subsequent therapy. The mean lymphocyte half-life calculated from these results was 7.8 mo.

Dose Estimations

The in vitro dose–response curve ($\alpha = 0.048$; $\beta = 0.031$) for HCC patients was used to estimate the ETBD delivered by both therapies. The mean and the SD on the mean (SDM) are presented in Figure 5. At the second time point, the ^{131}I-lipiodol therapy delivered an ETBD of 1.46 Gy (SD, 0.54), whereas the ^{188}Re-HDD/lipiodol therapy was responsible for 1.04 Gy (SD, 0.36; $P = 0.038$, Mann–Whitney).

Similar biodistributions were found for both ^{131}I-lipiodol and ^{188}Re-HDD/lipiodol. The total-body biologic half-life obtained from the total-body scans was 9.2 d (SD, 1.4) for ^{188}Re and 10.6 d (SD, 2.3) for ^{131}I ($P > 0.5$, Mann–Whitney).

Two weeks after ^{131}I-lipiodol therapy, the total-body, liver, and lung mean doses calculated from the total-body

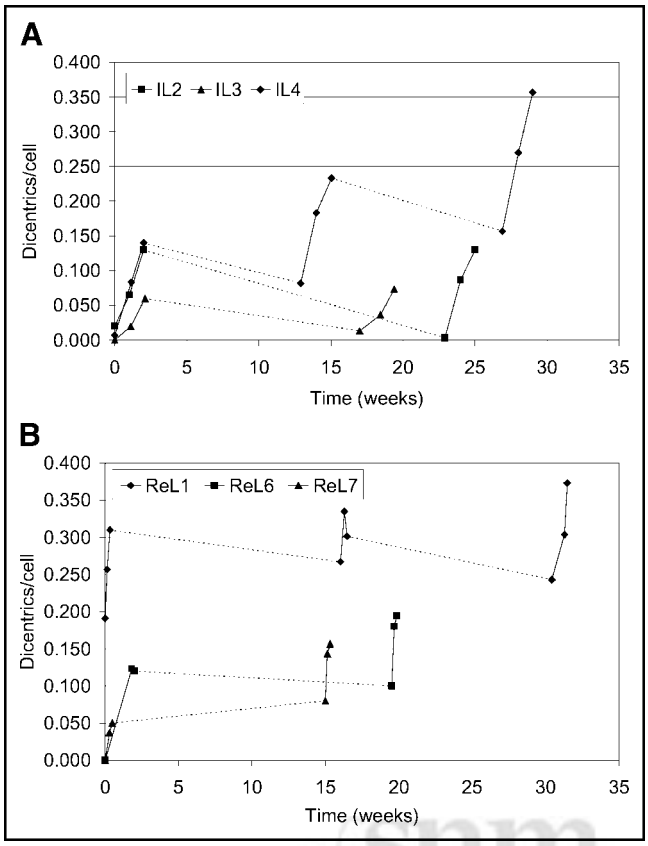

FIGURE 4. Time plot of DC yield in patients undergoing multiple subsequent therapies with ^{131}I-lipiodol (A) or ^{188}Re-HDD/lipiodol (B).

scans using the MIRD formalism were 0.67 Gy (SD, 0.12), 11.0 Gy (SD, 4.0), and 6.5 Gy (SD, 2.1), respectively. Two days after ^{188}Re-HDD/lipiodol administration, absorbed doses of 0.46 Gy (SD, 0.07), 6.8 Gy (SD, 2.1), and 4.4 Gy (SD, 1.0) were calculated for the total body, the liver, and the lungs, respectively. The absorbed dose to the blood, calculated from the doses to the liver, lungs, and remainder of the body using the percentage of blood in these compartments, was 1.56 Gy (SD, 0.34) 2 wk after ^{131}I-lipiodol therapy and 1.04 Gy (SD, 0.18) 2 d after ^{188}Re-HDD/lipiodol administration.

Blood Count Data

In the framework of the phase I study, information on blood cell counts was available for patients treated with ^{188}Re-HDD/lipiodol. The white blood cell (WBC) and thrombocyte counts versus time after administration are depicted in Figure 6. Except for patient ReL6, no major drop in WBC count was observed. The high increase in the WBC count of patient ReL1 2 wk after the first therapy was explained by enteritis. The low values in patient ReL2 were due to the HCC. In general, the WBC count tends to decrease slightly with time. Most patients (9/11) started therapy with thrombocyte counts less than $150 \times 10^3/\mu L$. Except for patient ReL3, no major fluctuations in thrombocyte counts were noted. The high WBC decrease noted in patient ReL6 was less pronounced in the thrombocyte count.

DISCUSSION

During the last few years, ^{131}I-lipiodol as a treatment for HCC has attracted much attention because of the promising results that have been achieved. The ^{131}I radioisotope has, however, significant constraints. An ideal radiotherapeutic agent should have good stability, high-energy β-radiation, and low-energy γ-emission, giving a low radiation burden to nontarget organs but sufficient to allow imaging. In addition, good availability and low cost are important requirements (*13*). The 8-d physical half-life and the high γ-ray emission of ^{131}I make radioprotection difficult in ^{131}I-lipiodol therapy and lead to isolation of the patients for up to 7 d after therapy in certain European countries, to comply with national guidelines. Moreover, the use of higher administered activities of ^{131}I-lipiodol is limited by the radiation protection issues associated with the high-energy γ-radiation of ^{131}I. Among the alternative isotopes to avoid these drawbacks, ^{188}Re is an important candidate. The isotope has a short physical half-life of 17 h and a lower γ-ray emission, which decreases the isolation to a maximum of 2 d. Furthermore, ^{188}Re has a higher β-emission and can be eluted from an in-house ^{188}W/^{188}Re generator, recently available on demand. The use of an ^{188}W/^{188}Re generator system is cost-effective, since these generators have a long shelf-life, resulting in a very low cost per dose (*13*). Radiopharmaceuticals labeled with ^{188}Re have previously been used in the treatment of painful bone metastases, in the pretransplant treatment of leukemia patients, and in the prevention of coronary restenosis (*14–17*).

In this phase I study, the cytotoxic effects of ^{188}Re-HDD/lipiodol and ^{131}I-lipiodol therapy were compared. To assess

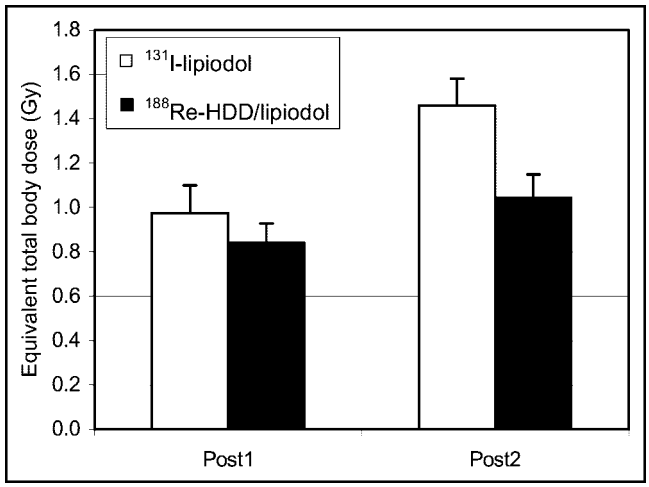

FIGURE 5. Comparison of the ETBD between ^{131}I-lipiodol and ^{188}Re-HDD/lipiodol at 1 and 2 wk after administration for ^{131}I-lipiodol and at 1 and 2 d after administration for ^{188}Re-HDD/lipiodol. Error bars represent the SD on the mean (SDM).

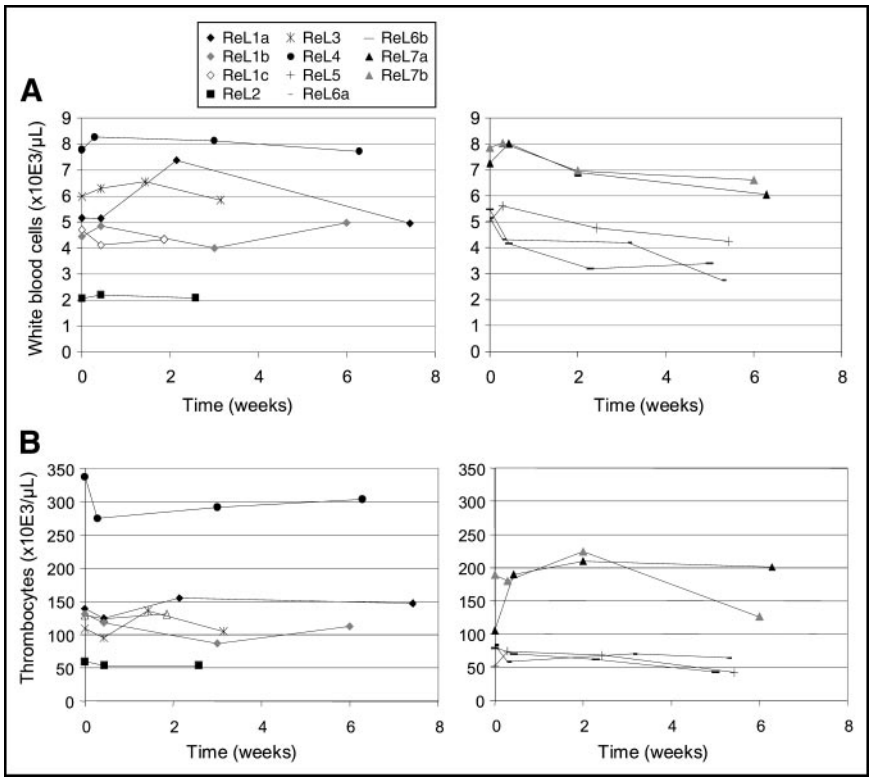

FIGURE 6. Plot of the WBC (A) and thrombocyte (B) counts vs. time after ^{188}Re-HDD/lipiodol administration.

cytotoxicity, the standard technique of DC scoring in lymphocytes was used. Doses were estimated from the DC yields on the basis of the dose–response curve derived from blood samples of HCC patients. With respect to in vitro irradiation, HCC patients turned out to be more sensitive than a healthy population. This observation confirmed other authors' data indicating that a significant fraction of cancer patients show enhanced in vitro radiosensitivity (*18,19*). The use of patient-specific dose–response curves for total-body dose estimation is therefore important. ^{188}Re-HDD/lipiodol treatment induced significantly fewer DCs than did ^{131}I-lipiodol therapy. Consequently, the ETBD delivered by the ^{188}Re-HDD/lipiodol therapy was lower than that delivered by the ^{131}I-lipiodol therapy for administered activities of 3.56 GBq and 1.89 GBq, respectively. After the chosen time points, 51 h for ^{188}Re and 14 d for ^{131}I, and with an effective half-life of 15.7 h for ^{188}Re and 4.6 d for ^{131}I, the percentage of the total cumulative activity considered was 89% and 88%, respectively. The total patient dose due to the ^{188}Re-HDD/lipiodol therapy was thus significantly lower than that due to the ^{131}I-lipiodol therapy for the activities administered.

A MIRDOSE calculation of the self-dose S values for 5-cm-diameter spheric nodules representing the tumor, combined with the effective half-life values obtained, shows that ^{188}Re-HDD/lipiodol and ^{131}I-lipiodol may be expected to have the same biologic effect on the tumor when the administered ^{188}Re activity is 60% higher than the ^{131}I activity. In this calculation, the biologic effect of the difference in dose rate between both isotopes resulting in the same total tumor dose was taken into account based on the isoeffect curve for different dose rates used in brachytherapy (*20*). In our phase I trial, 3.56 GBq of ^{188}Re-HDD/lipiodol and 1.89 GBq of ^{131}I-lipiodol were administered. For these activity values, the tumor radiation response is expected to be higher for the ^{188}Re-HDD/lipiodol therapy. Nevertheless, total-body doses for ^{188}Re-HDD/lipiodol were significantly lower, as can be explained by the lower γ-radiation component of ^{188}Re. Similar results were obtained by physical dosimetry using the MIRD formalism (^{188}Re: 0.42 Gy; ^{131}I: 0.67 Gy). The fact that the doses of the MIRD calculation are about half the biologically estimated doses (^{188}Re: 1.04 Gy; ^{131}I: 1.46 Gy) can be explained by the inhomogeneous distribution of blood throughout the body. In fact, in lipiodol therapy, significant activity accumulates in the liver and lungs. Because of the high absorbed doses in these organs and the large percentage of the blood pool inside, the total-body absorbed dose cannot be used as a physical estimate of the biologic ETBD. However, the absorbed dose to the blood, obtained from physical dosimetry, is in perfect agreement with the results from biologic dosimetry.

For total-body exposures of about 1 Gy, a slight decrease of approximately 20% in the WBC count and 30% in the platelet count is expected (*21*). Our patient group treated with ^{188}Re-HDD/lipiodol showed a decrease in this range. On the basis of the ECOG Common Toxicity Criteria scale (version 2.0, revised 1999), this decrease is not alarming. Two patients reach a scale 3 for the thrombocyte counts, but

these patients already had very low thrombocyte counts before therapy.

CONCLUSION

The present study showed that, compared with ^{131}I-lipidol therapy, ^{188}Re-HDD/lipiodol therapy yields a significantly lower cytotoxic effect and lower radiation exposure for an expected higher tumor-killing effect. ^{188}Re is an excellent alternative for ^{131}I in the internal radiation therapy of HCC with lipiodol. ^{188}Re allows higher administered doses, reduces radiation-protection problems, and improves patients' quality of life by shortening hospitalizations. The application of this new therapeutic agent for HCC will be investigated further in a dose-escalation study.

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REFERENCES

1. Badvie S. Hepatocellular carcinoma. *Postgrad Med J.* 2000;76:4–11.
2. Garin E, Laffont S, Rolland Y, et al. Safe radiation exposure of medical personnel by using simple methods of radioprotection while administering ^{131}I-lipiodol therapy for hepatocellular carcinoma. *Nucl Med Commun.* 2003;24:671–678.
3. Lau W, Leung T, Ho S, et al. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomized trial. *Lancet.* 1999;353:797–801.
4. Monsieurs MA, Bacher K, Brans B, et al. Patient dosimetry for ^{131}I-lipiodol therapy. *Eur J Nucl Med Mol Imaging.* 2003;30:554–561.
5. Brans B, Bacher K, Vandevyver V, et al. Intra-arterial radionuclide therapy for liver tumours: effect of selectivity of catheterization and ^{131}I-lipiodol delivery on tumour uptake and response. *Nucl Med Commun.* 2003;24:391–396.
6. *Annals of the ICRP: Publication 38—Radionuclide Transformations, Energy and Intensity of Emissions.* Oxford, U.K.: Pergamon; 1983.
7. Sundram FX, Jeong JM, Zanzonico P, et al. Trans-arterial rhenium-188 lipiodol in the treatment of inoperable hepatocellular carcinoma: an IAEA sponsored multi-centre phase 1 study. *World J Nucl Med.* 2002;1:5–11.
8. Lee YS, Jeong JM, Kim YJ, et al. Synthesis of ^{188}Re-labelled long chain alkyl diaminedithiol for therapy of liver cancer. *Nucl Med Commun.* 2002;23:237–242.
9. Sundram F, Chau TC, Onkhuudai P, Bernal P, Padhy AK. Preliminary results of transarterial rhenium-188 HDD lipiodol in the treatment of inoperable primary hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging.* November 19, 2003 [Epub ahead of print].
10. *Cytogenetic Analysis for Radiation Dose Assessment.* Vienna, Austria: IAEA; 2001:1–127.
11. Stabin MG. MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med.* 1996;37:538–546.
12. Snyder WS, Cook MJ, Nasset ES, et al. *Report of the Task Group on Reference Man.* New York, NY: Pergamon Press; 1974:1–272. ICRP Publication 23.
13. Wang SJ, Lin WY, Chen MN, et al. Radiolabelling of lipiodol with generator-produced ^{188}Re for hepatic tumor therapy. *Appl Radiat Isot.* 1996;47:267–271.
14. Palmedo H, Guhlke S, Bender H, et al. Dose escalation study with rhenium-188 hydroxyethilidene diphosphonate in prostate cancer patients with osseus metastases. *Eur J Nucl Med.* 2000;27:123–130.
15. Li S, Liu J, Zhang H, et al. Rhenium-188 HEDP to treat painful bone metastasis. *Clin Nucl Med.* 2001;26:919–922.
16. Bunjes D, Buchmann I, Duncker C, et al. Rhenium-188-labeled-antiCD66 (a, b, c, e) monoclonal antibody to intensify the conditioning regimen prior to stem cell transplantation for patients with high risk acute myeloid leukemia or myelodysplastic syndrome: results of a phase II study. *Blood.* 2001;98:565–572.
17. Kotzerke J, Hanke H, Hoher M. Endovascular brachytherapy for the prevention of restenosis after angioplasty. *Eur J Nucl Med.* 2000;27:223–236.
18. Terzoudi GI, Jung T, Hain J, et al. Increased G2 chromosomal radiosensitivity in cancer patients: the role of cdk1/cyclin-B activity level in the mechanisms involved. *Int J Radiat Biol.* 2000;76:607–615.
19. Baeyens A, Thierens H, Claes K, et al. Chromosomal radiosensitivity in breast cancer patients with a known or putative genetic predisposition. *Br J Cancer.* 2002;87:1379–1385.
20. Steel GG. The dose-rate effect: brachytherapy. In: Steel GG, ed. *Basic Clinical Radiobiology.* London, U.K.: Edward Arnold Publishers; 1993,120–129.
21. Mettler FA, Upton AC. *Medical Effects of Ionizing Radiation.* Philadelphia, PA: W.B. Saunders Co.; 1995:264–266.