Pharmacokinetics and Scintigraphy of Indium-111-DTPA-MOC-31 in Small-Cell Lung Carcinoma

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Radiolabeled MOC-31 retains its immunoreactivity and shows good in vivo immunolocalization to human SCLC xenografted in nude rats. **Methods:** We evaluated the immunotargeting properties and safety of ^{111}In-labeled monoclonal antibody (MAb) MOC-31 (125 MBq, 5 mg) in six patients with histologically proven small-cell lung cancer (SCLC). Scintigraphy and pharmacokinetics were performed up to 3 days after injection. **Results:** No adverse reactions were found after injection of MAb MOC-31. Pharmacokinetics obtained from plasma radioactivity showed plasma disappearance described most properly by a monoexponential model with a mean half-life value of 17.0 ± 1.4 hr. HPLC analysis documented the monomeric MOC-31 without evidence of immune complexes or radioactive lower molecular weight fractions. Mean 24-hr urinary excretion of radioactivity was 4.3% of the injected dose. Scintigraphy detected primary tumor or metastases in five of six patients. Localization of radioactivity in normal tissue was restricted, but additional experiments need to be performed to elucidate possible cross-reactivity of MOC-31 with normal tissue in vivo. **Conclusion:** Preliminary results justify further studies to reveal the possible usefullness of radiolabeled MOC-31 in the therapeutic and diagnostic management of SCLC.

Key Words: immunotargeting; indium-111-MOC-31; small-cell lung cancer

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Radiolabeled monoclonal antibodies (MAbs) directed against tumor antigens are of great interest in the diagnosis and therapy of cancer (*1*). Although lung cancer has been a leading cause of death in many countries for the past four decades, only a few studies have been published using radiolabeled MAbs for either radioimmunoscintigraphy (RIS) or radioimmunotherapy (RIT) in this type of cancer (*2,3*). Lung cancer can be divided into small-cell lung carcinoma (SCLC) and non-SCLC (*4*). SCLC comprises 25% of all newly diagnosed lung cancer cases and is characterized by high metastatic capacity, high proliferation rate and high initial sensitivity to chemo- or radiotherapy. Despite good initial response to chemo- or radiotherapy, almost all of the responding patients relapse within 1–2 yr with therapy-resistant recurrences. As a result, 5-yr survival is extremely low (*5,6*). Because of this bad prognosis, additional treatment modalities are needed. Radiolabeled MAbs might be a helpful addition.

A number of MAbs directed against SCLC-associated antigens have been developed and tested during the past years. These MAbs have been shown to be useful for immunohistochemical visualization of SCLC in tissue sections (*5–12*). One of these MAbs, MOC-31, which has been clustered as an SCLC-cluster 2 antibody during the First International Workshop on Small-Cell Lung Cancer Antigens, London, U. K., detects the pancarcinoma/epithelial glycoprotein EGP-2 (*13*).

Radiolabeled MOC-31 (^{111}In-DTPA-MOC-31) retains its immunoreactivity and shows good in vivo immunolocalization to human SCLC xenografted in nude rats (*14*).

In this article the pharmacokinetics and radioimmunolocalizing properties to primary tumor, metastases and normal tissues of ^{111}In-DTPA-MOC-31 was studied in SCLC patients.

MATERIALS AND METHODS

Patients

The study was approved by the Dutch Regulatory Authorities on Sera and Vaccins and by the local Medical Ethics Committee. Prior to study entry, each patient gave informed consent. The initial evaluation of all patients included physical examination, complete blood cell count, serum chemistries, chest radiography, CT of the chest, bronchoscopy and crista biopsy. All eligible patients had histologically proven SCLC positive for MOC-31. Staging procedures showed that one patient had limited disease and five extensive disease. One patient with extensive disease had a local relapse. Patients received an intravenous bolus injection with approximately 125 MBq (110–150 MBq) ^{111}In-DTPA-MOC-31 (4.0–6.3 mg). The occurrence of possible immediate

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and/or delayed adverse reactions in the patients was followed by regular physical examination and observation for at least 5 days.

Production of MOC-31

The murine MAb MOC-31 is an IgG1 antibody directed against the EGP-2 membrane antigen. The MOC-31 antibodies were generated by fusing SP2-0 myeloma cells and spleen cells of BALB/C mice immunized with a human SCLC-derived cell line (GLC 28). Hybridoma cells producing MAb MOC-31 were cultured in a Acusyst-Jr hollow-fiber bioreactor by Euroclone (Amsterdam, The Netherlands).

MOC-31 was purified using the BioPilot System (Pharmacia, Uppsala, Sweden) by cation-exchange chromatography (S-Sepharose Fast Flow), dialyzed against 10 m*M* potassium phosphate buffer (pH 6.0) and stored at a concentration of 7.12 mg IgG/ml at −20°C.

Purity of the MOC-31 preparation was checked by SDS-PAGE gradient gel electrophoresis (5%–15%) and isoelectric focusing (pH gradient of pH 3–9) using the Phast System (Pharmacia, Uppsala, Sweden) according to the manufacturer's procedures. The preparation proved to contain more than 95% pure MOC-31.

The preparation was tested for the presence of mouse derived viruses (mouse antibody production test) and mycoplasma according to the requirements of the Dutch Authorities on Sera and Vaccins by the ICLAS Virus Reference Centre (Nijmegen, The Netherlands) and found to be free of such contaminants.

For the start of the clinical study the preparation was aliquoted and formulated into glass vials under aseptic conditions and stored at 4°C until used for conjugation and labeling. Subsequent quality testing of formulated MOC-31 included determination of the protein concentration by OD_{280} (5.6 mg/ml). Physical state of the IgG was determined by size-exclusion high-performance liquid chromatography (SE-HPLC) (LKB.LCC 2252/UWM 2141, Pharmacia, Uppsala, Sweden; Bio Sil TSK-400 size-exclusion column; 300 × 7.8 mm, Bio-rad, Richmond, CA) and was found to be a homogeneously eluting single protein. The preparation had a pH of 7.4, an osmolality of 320 mOsm, whereas the preparation was sterile and free of pyrogens and acute toxicity as tested according to the Dutch Pharmacopoeia.

Radiopharmaceuticals

Conjugation of MOC-31 with DTPA-anhydride was done for every new patient essentially in accordance to the protocol by Hnatowich et al. (*15*) at a DTPA-anhydride: MAb ratio of 5:1. A 0.1-ml suspension of the DTPA-anhydride (Sigma, St. Louis, MO) in dry chloroform (1.0 mg/ml) was transferred in a glass tube and the chloroform was evaporated under a nitrogen stream. 1.5 ml of MOC-31 [5.6 mg/ml in 50 m*M* phosphate-buffered Saline, pH 7.4 (PBS)], was subsequently added and gently mixed at room temperature (RT) for 5 min. This mixture is later referred to as "unpurified conjugation mixture." DTPA-MOC-31 conjugate was separated from free DTPA by gel-filtration chromatography on a sterile and pyrogen-free column 1 × 22.5 cm acrylamide desalting column (Clinetics, Inc., Tustin, CA) using 0.1 *M* sodium acetate in 0.9% (w/v) NaCl (pH 5.0) as an eluant. Assessment of the number of molecules DTPA per molecule MOC-31 (see below) and radiolabeling were performed immediately after preparation.

Radiolabeling was done as follows: 500 μl $^{111}InCl_3$(37 MBq/0.02 μg; 0.04 *M* HCl in 0.1 ml, Amersham U.K.) was added to 50 μl of 1.0 *M* sodium acetate, (pH 9.2), resulting in a pH value of 5 to 5.5. Subsequently, 5–8 mg DTPA-MOC-31 was added and this was incubated at RT for 30 min. The reaction mixture was quenched with a 20-mM DTPA solution in 0.1 *M* sodium acetate over a period of 10 min. Radiolabeled ^{111}In-DTPA-MOC-31 was purified from free ^{111}In by gel-filtration chromatography on a sterile and pyrogen-free column as described above using 0.9% (w/v) NaCl as an eluant. Indium-111-DTPA-MOC-31 was subsequently filter-sterilized (0.22 μm filter, Millex GV) and immediately used for further experiments.

Quality Control of Indium-111-DTPA-MOC-31

The molar ratio of DTPA to MOC-31 in the conjugates was determined. Briefly, 5 μl of $^{111}InCl_3$ (37 MBq/0.02 μg; 0.04 *M* HCl in 0.1 ml, Amersham, UK) was added to a 50-μl sample of unpurified conjugation mixture and incubated for 30 min at room temperature. The distribution of ^{111}In between free DTPA and conjugated DTPA was determined by instant thin layer chromatography (ITLC) and size exclusion-high performance liquid chromatography (SE-HPLC) (see below). The distribution reflects the molar ratio of DTPA to MOC-31 in the conjugates. Radiochemical purity of the purified injected radiolabeled MOC-31 preparation was determined by ITLC and SE-HPLC.

ITLC was performed on silicagel impregnated glass fiber paper (Gelman Sciences, Ann Arbor, MI). The strip was developed with a solution made of 5 parts methanol, 4 parts NH_4-acetate (10% w/v) and 1 part 1.0 *M* citric-acid solution (pH 6.0). Radioactivity was determined by a chromatography scanner equiped with a NaI crystal.

HPLC was used to assay each labeled antibody preparation prior to administration. The HPLC system (LKB.LCC 2252/UWM 2141, Pharmacia, Uppsala, Sweden) was equiped with a Bio Sil TSK-400 size exclusion column (300 × 7.8 mm, Bio-rad, Richmond, CA). The column was eluted with PBS containing 5 m*M* DTPA. Radioactivity was detected by both an in-line detector made of a NaI crystal coupled to a multichannel analyzer programm (Ortec, Nieuwegein, The Netherlands) and by counting of collected 0.5-ml fractions using a gamma counter (KONTRON MR 1032 automated gammacounter, W + W Electronic Inc., Zurich, Switzerland). The same HPLC system but equipped with a Bio Sil TSK-250 size-exclusion column (300 × 7.8 mm, Biorad, Richmond, CA) was used to analyze plasma and urine samples.

The immunoreactive fraction of radiolabeled MOC-31 was essentially determined by cell binding assays as described by Lindmo et al. (*16*). SCLC cell-line GLC-28 was used for this assay (14). Cells were harvested by centrifugation and resuspended at a concentration of 1×10^7 cells/ml in PBS. A fixed amount of ^{111}In-DTPA-MOC-31 (0.05–0.1 μg) was added to increasing numbers of GLC-28 cells (ranging from 0.08×10^6 to 2.6×10^6 cells) in 2 ml PBS and incubated at room temperature for 30 min. Cells were centrifugated and washed three times with PBS. The immunoreactive fraction was calculated as the ratio of cell-bound (pellet obtained after the last centrifugation) to noncell-bound radioactivity (sum of the radioactivity measured in the supernatants).

Scintigraphy

Planar gamma camera images were obtained 2, 24, 48 and 72 hr after injection using a single-head gamma camera equipped with a parallel-hole, medium-energy collimator. Both 173 keV and 247 keV gamma-ray peaks of ^{111}In with symmetric 20% windows were used to record anterior and posterior views of the whole body, chest and abdomen, as well as lateral views of the head and other sides if considered relevant. Images included whole-body scans and scans from regions of interest such as the chest, abdomen and head. The scintigrams were interpreted by nuclear medicine specialists without prior knowledge of the extent of the disease.

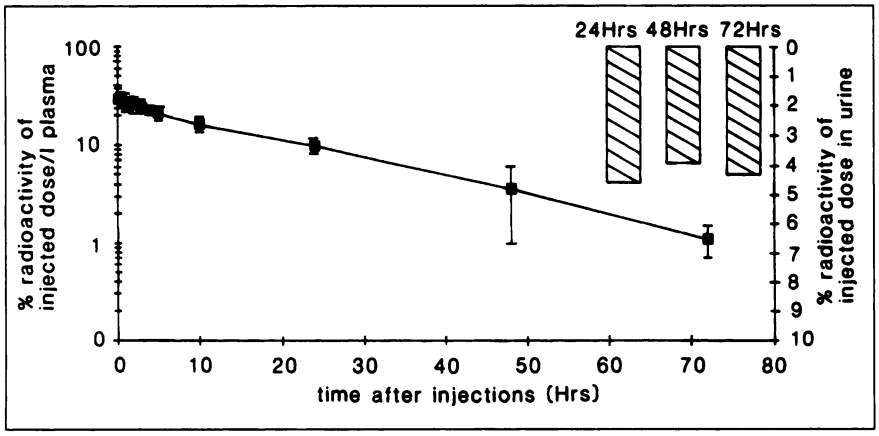

FIGURE 1. Plasma disappearance and 24-hr urinary excretion of total radioactivity expressed as percent radioactivity (mean ± sd) of injected dose in patients (n = 6) after intravenous injection of ^{111}In-DTPA-MOC-31.

Pharmacokinetic Studies

After injection of ^{111}In-DTPA-MOC-31, heparinized blood samples (5 ml) were drawn for pharmacokinetic studies at 15, 30 and 60 min; 2, 3, 5, 10 and 24 hr; and 2 and 3 days postinjection. Samples were centrifuged and the plasma was stored at 4°C until analysis. Radioactivity was determined in the plasma samples (1.0 ml) using a gamma counter. Results were expressed as the percentage of radioactivity of the injected dose per liter plasma after correction for radioactive decay. The pharmacokinetic profile was determined with the aid of a pharmacokinetic software program (MW/PHARM; Mediware Groningen, The Netherlands). The equation describing the decline of the percent radioactivity of the injected dose per liter plasma-time curve was derived by nonlinear regression analysis using a weighted least-squares simplex algorithm. Urine was collected as 24 hr pools during the first 3 days and radioactivity was determined in 2-ml samples and expressed as the percent injected dose excreted in urine per 24 hr. In addition, plasma samples collected 1, 2 and 3 days after injection, as well as all urine samples, were analyzed by SE-HPLC.

RESULTS

Labeling and Quality Control

Conjugation of MOC-31 with DTPA-anhydride resulted in a molar ratio DTPA: MOC-31 of 0.5–1.5. Subsequent labeling with $^{111}InCl_3$ resulted in labeling yields of about 65%. After further purification using gel-filtration chromatography, the radiochemical purity of the ^{111}In-DTPA-MOC-31 was >95%, except for labeling sample 6, which resulted in a radiochemical purity of 90%. The only detectable radiochemical impurity was ^{111}In-DTPA. The immunoreactive fraction of the purified, labeled product ^{111}In-DTPA-MOC-31 was above 0.70 in all patients.

Adverse Reactions

After injection of the ^{111}In-DTPA-MOC-31 preparation in the patients, no immediate or delayed adverse reactions were noted. Since it was not intended in this study to give repeated injections of antibody the development of human anti-mouse antibody (HAMA) response in the patients was not determined.

Pharmacokinetics (Plasma/Urine)

Plasma clearance of radioactivity could be described most properly by a monoexponential model and was similar for all patients (Fig. 1). The mean half-life value was 17.0 ± 1.4 hr. The radiochemical profile obtained by SE-HPLC at different time points (t = 1, 24, 48 and 72 hr after injection) showed only one peak corresponding to intact IgG (150,000 Da). Apparently no radioactive high molecular weight components (immune complexes) nor low molecular weight fractions (catabolites) were present in the plasma of these patients.

Mean 24-hr urinary excretion of radioactivity was 4.3% and ranged from 1.5% to 6.7% of injected dose (Fig. 1), except for Patient 6 (12.9% ID urine excretion in the first 24 hr). Radioactivity in urine was present as low molecular weight fractions (<1000 Da) as determined by SE-HPLC.

Scintigraphy

Scintigraphic studies were performed at different timepoints after injection of ^{111}In-DTPA-MOC-31 as indicated. Images with the lowest background activity and highest tumor uptake were obtained 48 to 72 hr after injection. Table 1 summarizes the scintigraphic results obtained 48 hr postinjection.

Case Reports. All patients were suffering from histological proven SCLC positive for MOC-31. Lesions were clearly

TABLE 1
Scintigraphic Results

Patient no.	Number of metastases indicated by standard diagnostic procedures	RID of primary tumor	Number of metastases detected by RID
1	3	+	3
2	0	+	0
3	5	−	3
4	3	+	2
5	2	+	1
6*	8	+	5

*In Patient 6, several previous (CT/radiograph) unknown metastases were detected by ^{111}In-DTPA-MOC-31 scintigraphy: liver (3×), right lung (3×) and left lung (2×). Figures not included.
RID = radioimmunodetection.

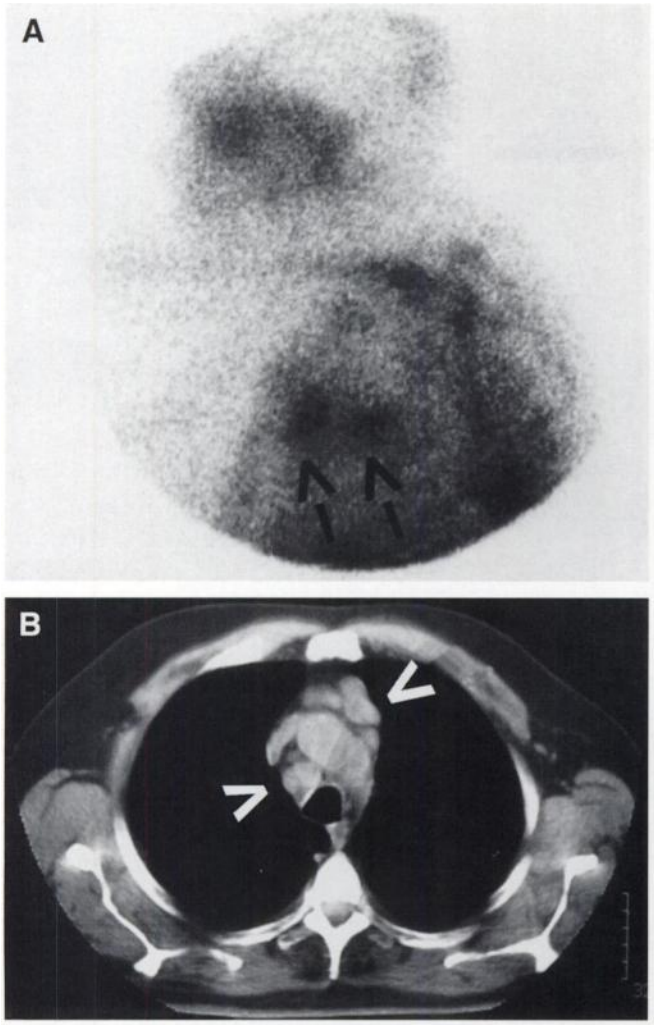

FIGURE 2. (A) Left lateral view of the chest (Patient 1) 48 hr postinjection of ^{111}In-DTPA-MOC-31. The two hot spots indicate two mediastinal metastases (arrow). (B) CT scan shows two mediastinal metastases (arrow) corresponding with the hot spots on the scintigram in Figure 2A.

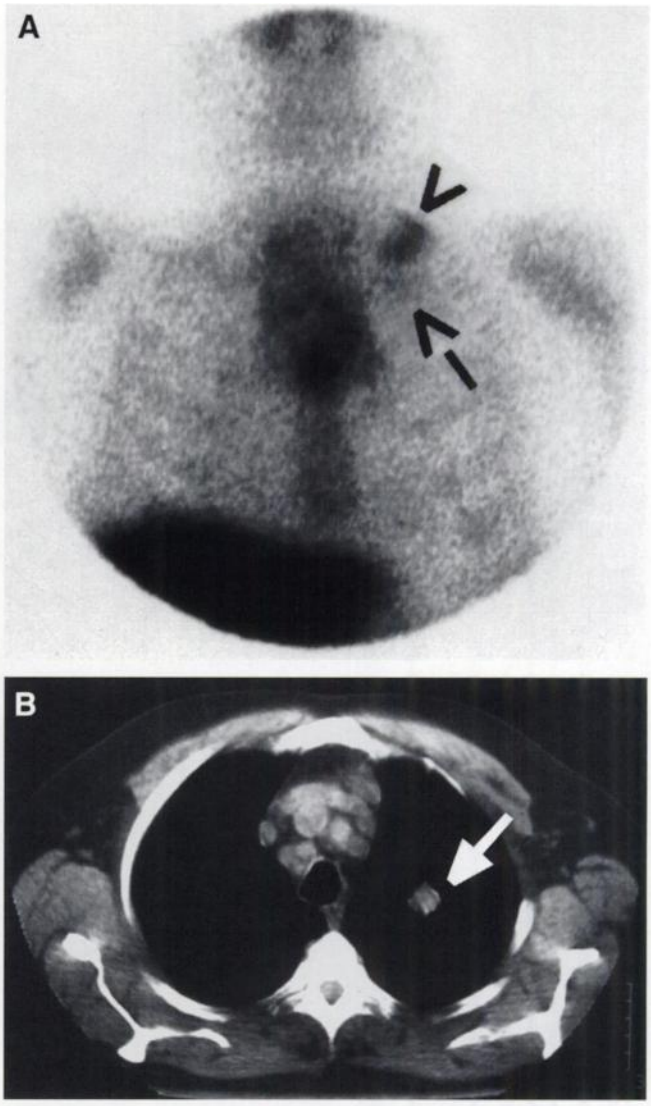

FIGURE 3. (A) Anterior view of the chest (Patient 1) 48 hr postinjection of ^{111}In-DTPA-MOC-31. The hot spots represent the primary tumor (arrow) and the left supraclavicular metastasis (arrow head). (B) CT scan indicates primary tumor (arrow) corresponding with the hot spot on the scintigram shown in Figure 3A.

identified by the diagnostic modalities described in Materials and Methods.

Patient 1 had limited disease and a primary tumor in the upper lobe of the left lung, a lymph node metastasis in the left supraclavicular fossa and two metastases in the mediastinum. Scintigraphy showed two regions (mediastinal and supraclavicular) with increased accumulation of radioactivity 24 hr after injection. After 48 hr, additional scintigraphy revealed two spots representing mediastinal metastases which were clearly visible on the lateral scan (Fig. 2A). The corresponding CT scan is shown in Figure 2B. The other spots represented the primary tumor in the left lung and the left supraclavicular metastasis (Fig. 3A). The corresponding CT scan is shown in Figure 3B.

Patient 2, who had extensive disease, received prior chemotherapy and had complete response but relapsed locally from SCLC in the right upper lung. Scintigraphy showed activity at the right hilum.

Patient 3, who also had extensive disease, had a primary tumor in the left main bronchus and suspected mediastinal, supraclavicular (both sides) and axillary (both sides) lymph node metastases. Three of these six lesions could be clearly detected scintigraphically. Both the mediastinal and the supraclavicular lymph nodes were detected, whereas the primary tumor was not visible. In fact, the left lung did not show any uptake of radioactivity, which might indicate poor vascularization in that region. Also, both axillary lymph node metastases did not show uptake of radioactivity.

Patient 4 also had extensive disease and had a primary tumor in the left upper lung (hilus) and metastases in the mediastinal lymph nodes, left parotid gland and in the bone marrow. Of these, the primary tumor and the parotic and mediastinal lesions were detectable (Fig. 4A,B). The corresponding thorax radiograph is shown in Figure 4C. Metastases in the bone marrow could not be detected scintigraphically

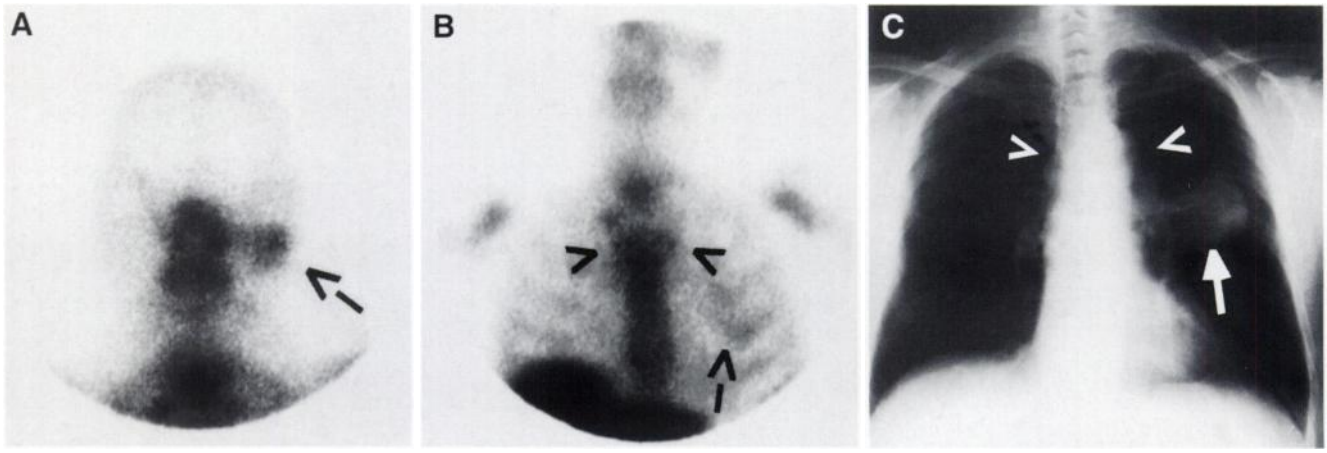

FIGURE 4. (A) Anterior view of the head (Patient 4) 48 hr postinjection of ^{111}In-DTPA-MOC-31 shows uptake in a metastasis in the parotid gland (arrow). (B) Anterior view of the chest obtained 48 hr postinjection of ^{111}In-DTPA-MOC-31 shows uptake in primary tumor (arrow) and mediastinal lesions (arrow head). (C) Thorax radiograph (anterior) indicates primary tumor (arrow) and mediastinal lesions (arrow head) corresponding with the lesions shown on the scintigram in Figure 4B.

because ^{111}In uptake in bone marrow obscured any specific accumulation of ^{111}In-labeled MAbs.

Patient 5, who had extensive disease, had a primary tumor in the left upper lung (hilus) and metastases in the left supraclavicular and mediastinal lymph nodes. The supraclavicular metastasis was clearly detectable by scintigraphy, whereas only minimal activity was present in both the primary tumor and the mediastinal metastases.

Patient 6, who also had extensive disease, had a primary tumor in the right upper lobe of the lung, metastases were present in paramediastinal and retroperitoneal lymph nodes, furthermore the head of the pancreas, in the hilus of the spleen, both adrenals and, in addition, at two skin locations. Scintigraphy showed the primary tumor in the right upper lobe. Both skin metastases were very prominently detectable. Furthermore, three spots were seen corresponding to accumulation of radioactivity in the middle lobe of the right lung as well as two spots in the left lung. Increased accumulation of radioactivity was also present in the paramediastinal region and in the left adrenal and hilus of the spleen (Fig. 5). Additionally, three hot spots were detectable in the liver. One of these is clearly visible in the scintigram shown in Figure 5.

Overall, the scintigraphic studies showed radioactivity in the blood pool, which was detected early after injection, but rapidly cleared, corresponding with the relatively short plasma half-life of 17 hr.

Radioactivity uptake in normal tissues such as the gut, kidney, bone marrow, spleen and liver were detected whereas the magnitude of radioactivity changed from tissue to tissue. Gut uptake showed a pattern of small intestine and colon. This pattern changed in time suggesting uptake in the fecal stream. Radioactivity uptake in the bone marrow, spleen and liver was seen 24 hr after injection and persisted with time. Kidney uptake was particularly apparent in the late images (72 hr p.i.).

To illustrate radioactivity uptake in normal tissues in time, a series of sequential images of Patient 1 is presented in Figure 6.

DISCUSSION

We examined the safety, pharmacokinetics and radioimmunolocalization of ^{111}In-DTPA-MOC-31 in patients with histologically proven SCLC. Indium-111-DTPA-MOC-31 did not induce any adverse reaction in our study in which a single injection of the radiolabeled antibody was given at doses of 4.0 to 6.3 mg.

The pharmacokinetic study indicated that the plasma

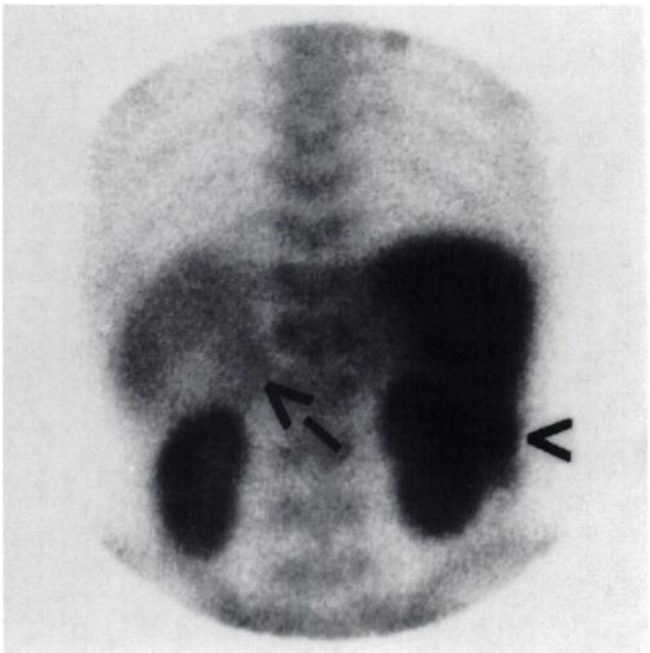

FIGURE 5. Posterior view of the lower thoracic and lumbal area (Patient 6), 48 hr after injection of ^{111}In-DTPA-MOC-31, shows increased uptake in the left adrenal and splenic region (arrow) as well as one lesion in the liver (arrow head).

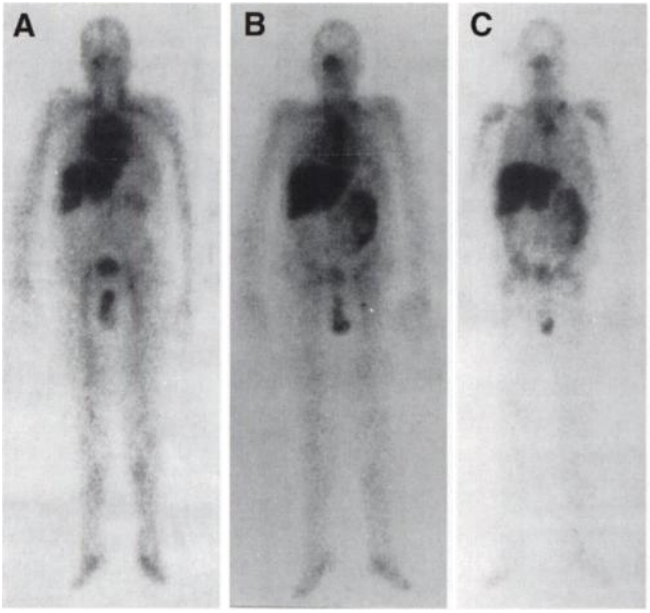

FIGURE 6. Series of sequential images of Patient 1 at 2 (A), 24 (B) and 48 (C) hr after injection of ^{111}In-DTPA-MOC-31 shows whole-body distribution of radioactivity.

disappearance curve of radiolabel could be described most properly by a monoexponential model and was found to be essentially similar for all patients (Fig. 1). The mean half-life value (± s.d.) was 17.0 (±1.4) hr, which is comparable to earlier reported plasma half-life values of mouse IgG [i.e., CO17-1A (*17*)]. Radiolabeled plasma half-life values can be influenced by a number of factors like the type of MAb, the presence of anti-mouse-IgG antibodies, high circulating antigen levels, existence of an accessable pool of antigen in normal tissues, metabolism of antibody and subsequent uptake in cells and also unstable chelation of the label. In vitro stability studies showed, that ^{111}In-DTPA-MOC-31 is stable up to 72 hr in PBS with and without challenging with DTPA. Stability studies in plasma showed transchelation up to 5%–10% per 24 hr (unpublished data). In the present study, transchelation and formation of ^{111}In-transferrin could not be determined in plasma samples using SE-HPLC. No indications were found for the presence of small molecular weight fractions in plasma.

SE-HPLC of plasma, isolated from the patients at different time points after injection of radiolabeled antibody, did not show antigen-antibody or antibody-antibody complexes either. This result confirms an earlier report, that the antigen detected by MOC-31 does not occur in a soluble form in the plasma of SCLC patients, at least not to a high extent (*18*). Circulating antibody-antibody complexes (mol wt > 300,000 Da) were not expected within 3 days after injection because the patients were injected for the first time with mouse antibody. Urinary excretion of radioactivity was low and relatively constant up to 72 hr after injection. Excreted radioactivity was present in low molecular weight fractions (<1000 Da) as was shown by HPLC. It was not possible to discriminate ^{111}In-DTPA from ^{111}In-peptide fractions. Catabolically generated (radio-labeled) peptides with a molecular weight similar to DTPA conjugated ^{111}In may be formed due to aspecifically trapped antibody in the liver and subsequently excreted by the kidney (*19–22*). The higher urinary excretion in the first 24 hr after injection in Patient 6 (12.9%) probably resulted from free ^{111}In-DTPA in the administered material since this finding corresponded well with the lower radiochemical purity of the preparation (90%). In this patient, urinary excretion returned at later timepoints to values corresponding to those found in the other patients.

Tumor localization was seen in most of the patients, both in primary tumors (5 of 6) and in metastatic lesions (14 of 21 known metastases) and did correspond with lesions seen on the matching CT scan and radiographs. In all patients, SCLC was also histologically confirmed and shown to be positive for MOC-31 antigen expression. Localization persisted at least up to 72 hr after injection, indicating specific binding. In Patient 6, increased uptake of label in unknown lesions was detected in the lung and even in the liver. The latter increased uptake appeared as hot spots on the scintigrams, which corresponded to metastases as was subsequently confirmed by liver ultrasound. Detection of metastatic lesions in liver using ^{111}In-labeled MAbs is often difficult because high uptake of ^{111}In-related radioactivity in liver is encountered.

The uptake in normal epithelial tissues of in vivo applied MOC-31 is of great importance for evaluating the prospects of immunoscintigraphy and future immunotherapy with this antibody, because these tissues are known to be radiosensitive (Fig. 6).

Uptake of radioactivity, especially in the spleen, bone marrow and liver is frequently seen with ^{111}Indium-labeled antibodies and may be related to metabolism of the antibody and subsequently intracellular localisation of ^{111}In-labeled small molecular weight products. Another possibility is the release of ^{111}In due to the instability of DTPA conjugated antibodies in vivo. It is known that DTPA-MAb can release 15% of the ^{111}In per 24 hr, which is transchelated to transferrin and deposited as ferritin in different organs (*19–24*). A considerable degree of uptake in kidneys was seen also in the late images (72 hr postinjection). This uptake can be either antigen-related uptake of ^{111}In from transferrin or clearance of ^{111}In containing low molecular weight conjugates. The latter is not quite obvious because mean 24 hr urinary excretion of radioactivity was low (4.3% of the radioactivity of the injected dose).

Uptake of radioactivity in the gut showed a scintigraphic pattern consistent with small intestine and colon uptake. This pattern proved to move in time postinjection, suggesting uptake in the fecal stream, which is known to occur with ^{111}In-labeled antibodies due to radiolabeled antibody metabolism in the liver with biliary excretion (*22*).

Although MOC-31 stains normal epithelia on tissue sections in vitro, normal epithelia such as the thyroid and respiratory tract and lung proved to be poorly accessible to ^{111}In-DTPA-MOC-31 in vivo. The apparently low accessi-

bility of normal epithelia as compared to malignant epithelial cells may be caused by the presence of an intact basal membrane which may form a barrier to mouse antibodies.

CONCLUSION

This study shows that MOC-31 can localize in patients with SCLC in vivo. Localization of the antibody in normal tissue is restricted and no adverse reactions were noted.

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