Experimental and Clinical Analysis of the Characteristics of a Chimeric Monoclonal Antibody, MOv18, Reactive with an Ovarian Cancer-Associated Antigen

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Monoclonal antibody (Mab) MOv18 preferentially reacts with gynecological carcinomas. We have analyzed the characteristics of murine MOv18 (m-MOv18) and chimeric MOv18 (c-MOv18). We found no differences in affinity and binding to IGROV1 cells between c-MOv18 as IgG and $F(ab')_2$ fragments and m-MOv18. In nude mice bearing IGROV1 xenografts, maximum tumor uptake 6–15 hr after i.v. injection of radiolabeled m-MOv18 IgG, c-MOv18 IgG, c-MOv18 $F(ab')_2$ and a control IgG, 2C7, was 10%, 11%, 3% and 4.5% of the injected dose/g (%ID/g), respectively. M- and c-MOv18 IgG retained this level for several days, while c-MOv18 $F(ab')_2$ and 2C7 cleared rapidly from the tumor. Uptake in normal tissues was low, with the exception of high uptake in kidneys for c-MOv18 $F(ab')_2$. Tumor/blood ratios for c-MOv18 $F(ab')_2$ were sixfold higher than for IgG. Radiation absorbed doses to tumor tissue delivered by 10 μCi iodinated m-MOv18 IgG, c-MOv18 IgG and c-MOv18 $F(ab')_2$ were 39 cGy, 49 cGy and 5 cGy, respectively. A cocktail of ^{125}I-c-MOv18 IgG and ^{131}I-c-MOv18 $F(ab')_2$ injected i.v. into an ovarian cancer patient, localized specifically in the tumor. Ovarian cancer tissue samples obtained 2 days postinjection showed a mean uptake of 12.2×10^{-3} and 2.7×10^{-3} %ID/g for c-MOv18 IgG and c-MOv18 $F(ab')_2$, respectively. Results from these in vitro and in vivo experiments indicate that c-MOv18 has promise as a Mab for clinical use.

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The use of rodent monoclonal antibodies (Mabs) for repeated administration in cancer treatment is hampered by the induction of an immune response in patients (*1*). The presence of human anti-mouse antibodies can reduce the uptake of the Mab in tumors and may also cause allergic reactions. Human Mabs may circumvent this problem and a recent immunoscintigraphic study with one of these Mabs has indeed shown the absence of an immune response (*2,3*). However, the generation of stable human hybridomas that generate Mabs of desired specificity is still a problem (*4*). Another way to reduce the immunogenicity of rodent Mabs is the use of recombinant DNA technology to generate chimeric Mab with a human constant region and a murine variable region (*5*). Only a few trials with chimeric Mabs have been performed and mostly with c-17-1A in patients with advanced colorectal cancer (*6–8*). The present results suggest that chimeric Mabs are less immunogenic and therefore are potentially useful for therapy.

Mab MOv18 preferentially reacts with gynecological carcinomas (*9,10*) and has been constructed in a chimeric form. Murine Mab MOv18 (m-MOv18) is an IgG1 immunoglobulin reactive with a 38 kDa glycoprotein present on the cell membrane. Recently, the target antigen was identified as a folate binding protein (*11,12*). No reactivity with normal tissues was observed, except for the epithelium of renal tubules, Fallopian tubes, pancreas, lung, salivary gland and endocervix. Immunoscintigraphic studies with ^{131}I-labeled m-MOv18 in ovarian cancer patients have shown promising results (*13*).

In this study, we compared the binding characteristics in vitro of the chimeric MOv18, both as IgG and as $F(ab')_2$ fragments, with those of the parental murine Mab MOv18. In addition, we studied the pharmacokinetics and biodistribution of m- and c-MOv18 in a human ovarian cancer xenograft model. Furthermore, we performed an immunoscintigraphic study in an ovarian cancer patient to obtain clinical biodistribution data of c-MOv18.

MATERIALS AND METHODS

Monoclonal Antibodies

Production and immunohistochemical characterization of the murine Mab MOv18 have been described earlier by Miotti et al. (*9*). M-MOv18 is an IgG1. C-Mab MOv18 was constructed by fusion of the variable regions of m-MOv18 with the human IgG1 constant regions by Dr. L.R. Coney (Centocor Inc., Malvern, PA). Mab 2C7 was used as a control antibody. This Mab reacts

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with human α-glucocerebrosidase and is also of the IgG1 isotype (*14*).

Ascitic fluid containing m-Mab MOv18 was provided by Dr. S.O. Warnaar (Centocor Inc., Leiden, Netherlands). Purification of the antibody was performed by affinity chromatography using Affi-Gel Protein-A MAPS II (Bio-Rad Laboratories, Utrecht, The Netherlands). Purified IgG and $F(ab')_2$ fragments of c-Mab MOv18 were also provided by Dr. Warnaar. Purified Mab 2C7 was provided by Dr. J.M. Tager (University of Amsterdam, Amsterdam, The Netherlands).

Cell Lines

IGROV1 is a human ovarian cancer cell line described by Bénard et al. (*15*). WiDr is a human colon cancer cell line described by Nogushi et al. (*16*) and was used as a negative control. Both cell lines were grown as a monolayer in Dulbecco's modified Eagle's medium (DMEM) obtained from Flow (Amsterdam, The Netherlands), supplemented with heat-inactivated 10% fetal calf serum (FCS).

Tissue culture cells were tested for reactivity with the Mabs in an immunofluorescence assay. Briefly, cells were incubated with an excess of the Mabs. After washing, bound Mab was detected with FITC-conjugated goat anti-mouse Ig (Sigma Chemical Co., St. Louis, MO) or rabbit anti-human IgG (Dakopatts, Glostrup, Denmark). For the c-MOv18 $F(ab')_2$ fragments, a $F(ab')_2$ specific anti-human conjugate was used (Sigma). All incubations were performed for 30 min at 0° C. Fluorescence staining was analyzed microscopically or with a FACSCAN cytofluorometer (Becton and Dickinson, Mountain View, CA).

Xenografts

IGROV1 and WiDr xenografts were established from 10^7 cells injected s.c. into both flanks of female, 8–10-wk old NMRI/Cpb (nu/nu) mice (Harlan/Cpb, Zeist, The Netherlands). Histology of IGROV1 xenograft tissue shows an undifferentiated carcinoma pattern. WiDr xenografts show the pattern of a poorly differentiated mucinous adenocarcinoma. The tumor volume doubling times for IGROV1 and WiDr xenografts were 7 and 8 days, respectively. The xenografts were transferred by implanting fragments of solid tumor tissue with a diameter of 2–3 mm s.c. through a small skin incision in subsequent recipients. Tumors were measured in three dimensions and the volume was expressed by the equation length × width × height × 0.5 in mm^3. Binding of Mabs and $F(ab')_2$ fragments to xenograft tissue was determined in an indirect immunoperoxidase assay as has been described earlier (*17*).

Radiolabeling of Antibodies and Fragments

Whole antibodies and fragments were labeled with either ^{125}I or ^{131}I by the iodogen one-vial method according to Haisma et al. (*18*). Free iodine was removed by an anion exchange resin suspension in PBS containing 1% BSA (AG1-X8, Bio-Rad, Utrecht, The Netherlands). The percentage of radioactive iodine bound to the Mab was determined by trichloroacetic acid (TCA) precipitation and was always >95%. The specific activities of the iodinated Mabs ranged from 1–6 mCi/mg.

Immunoreactivity and Affinity

After radiolabeling of the Mabs, the immunoreactive fraction was determined on IGROV1 cells according to Lindmo et al. (*19*). The apparent affinity constant of Mab c-MOv18 was determined on IGROV1 cells by incubating a fixed amount of radiolabeled Mab mixed with unlabeled Mab over a concentration range of 1 to 150 μg/ml. The cell-bound radioactivity was measured in a gamma counter. The affinity constant and the number of antigenic sites per cell were calculated from a Scatchard plot of specifically bound Mab versus bound over free Mab (*20*).

Pharmacokinetics and Biodistribution

In mice, thyroid uptake of iodine was blocked by addition of potassium iodine to the drinking water (0.1%) starting from three days before and until the end of the study. Tumor-bearing animals (tumor volume: 173 ± 97 mm^3) were injected with a tracer dose (5–10 μCi) of a mixture of one Mab labeled with ^{131}I and another Mab labeled with ^{125}I. Mice were killed at 1, 3, 6, 15, 24, 48, 72, 96 and 168 hr after injection. For each time point, three mice were used. Blood was collected from mice under ether anesthesia. Normal tissues and tumors were then dissected, rinsed in saline to minimize blood residues and dried. Blood and tissues were weighed and the radioactivity was measured in a 2-channel gamma counter with automatic correction for spillover of both radionuclides in the channels. To correct for radioactive decay, a standard solution of the injected material was prepared and counted simultaneously with the tissues at each time point studied. The results were expressed as the percentage of injected dose per gram (%ID/g). The proportion of radioactivity associated with protein in serum was determined by precipitation with 10% TCA.

Radiation Dose Measurements and Calculations

The approximate radiation doses to various tissues were derived from the uptake data of the conjugate in each tissue assuming uniform distribution of the radionuclide within the organs. The absorbed dose was then calculated using the trapezoid integration method for the area under the curve (AUC) (*21*). These doses were expressed in cGy by multiplying the integrated μCi.h/g by the g.cGy/μCi.h factor for ^{131}I (0.3985), published by the Medical Internal Radiation Dose committee (*22*). The gamma-radiation dose has been neglected as absorbed fractions in the small organs of the mouse are low. The initial concentration of the radiolabeled Mab in each organ was assumed to be 0 μCi/g.

Patient Study

A patient, 54 yr of age, presented with ascitic fluid and an irregular mass in the pelvic region, suspected of being ovarian cancer. After informed consent was obtained, the patient was injected intravenously with a combination of 5.0 mCi ^{123}I-c-MOv18 IgG, 47 μCi ^{131}I-c-MOv18 $F(ab')_2$ and 43 μCi ^{125}I-c-MOv18 IgG, according to a current clinical protocol. The total protein dose of Mab c-MOv18 was 3 mg. To prevent thyroid localization, sodiumperchlorate was given from the day before until one week after administration of the immunoconjugates. Planar anterior and posterior immunoscintigrams of the abdomen were performed 1, 4 and 24 hr after injection of the radiolabeled Mabs with a single-head gamma camera (Gemini 700, General Electric) equipped with a low energy collimator. Blood samples were taken 5, 10, 30 and 60 min and 1, 2, 4, 6, 8, 24, 30 and 48 hr after administration. Explorative laparotomy took place two days after injection of the immunoconjugates.

Both ovaries showed tumor tissue; ovaries, uterus and the omentum were removed. Multiple peritoneal metastases were present and removed where possible. Biopsies were taken also from normal tissues, like muscle, fat, peritoneum and skin. After weighing, the amount of radioactivity in the biopsies was determined and the uptake was expressed as the %ID/g as described

for the mouse study. Thereafter, all samples were examined microscopically to determine the presence of malignant cells.

RESULTS

In Vitro Characteristics of Mabs

Mab MOv18 was tested on live IGROV1 cells. A distinct membrane staining was visible and no differences in staining were observed between c-MOv18 and m-MOv18 (not shown). Also, equal reactivity was observed for c-MOv18 as IgG and as $F(ab')_2$ fragments. The control Mab 2C7 did not react with IGROV1 cells. The m- and c-MOv18 Mabs were tested for reactivity on sections of IGROV1 xenograft tissue by immunoperoxidase staining. Staining was intense and homogeneously distributed. The binding was mainly detectable on the cell membrane. No differences were observed between m-MOv18 and c-MOv18 or between IgG and $F(ab')_2$ fragments of c-MOv18.

After iodination of m-MOv18 IgG, c-MOv18 IgG and c-MOv18 $F(ab')_2$ fragments, the immunoreactive fractions (mean ± s.d.) were 54.1% ± 3.9%, 59.5% ± 4.5% and 56.5% ± 5.5%, respectively. A Scatchard analysis was performed with the radiolabeled c-Mab on IGROV1 cells. The apparent affinities for c-MOv18 IgG and $F(ab')_2$ fragments were calculated to be 5.2×10^9 M^{-1} and 5.8×10^9 M^{-1}, respectively. For both forms, the cells expressed 2×10^5 antigenic sites per cell.

Pharmacokinetics of Mabs and Fragments

IGROV1-bearing mice were injected with a combination of either ^{131}I-labeled m-MOv18 IgG plus ^{125}I-control Mab 2C7 or with ^{131}I-labeled c-MOv18 IgG plus ^{125}I-labeled c-MOv18 $F(ab')_2$ fragments. With the tracer doses used, competition for antigenic binding sites between the IgG and $F(ab')_2$ fragments is not relevant. Figure 1A shows the pharmacokinetics of the radiolabeled IgGs and $F(ab')_2$ fragments in the blood. The alpha half-lives of m-MOv18 and c-MOv18 IgG measured 21 hr and 9 hr, respectively. The respective beta half-lives measured 85 hr and 61 hr. $F(ab')_2$ fragments of c-MOv18 were cleared from the circulation within 4 hr. The clearance pattern of the control Mab was similar to that of m-MOv18 IgG. The amount of free iodine in the serum, measured at each time point was <5%. Analysis of the serum samples with Superose-6 or Superose-12 FPLC chromatography at 3 hr and 15 hr did not indicate the formation of immune complexes or degradation products, and the radioactivity peaks corresponded to that of respectively IgG and $F(ab')_2$ fragments (not shown).

Biodistribution of Mabs and Fragments

The uptake of radiolabeled Mabs in the IGROV1 tumors is visualized in figure 1B. The maximum %ID/g tumor tissue for m-MOv18 IgG, c-MOv18 IgG and c-MOv18 $F(ab')_2$ fragments was 10%, 11% and 3%, respectively, and these amounts were reached at 6–15 hr after injection. For m- and c-MOv18 as IgG, tumor tissue uptake was retained at this high level for 2 and 6 days,

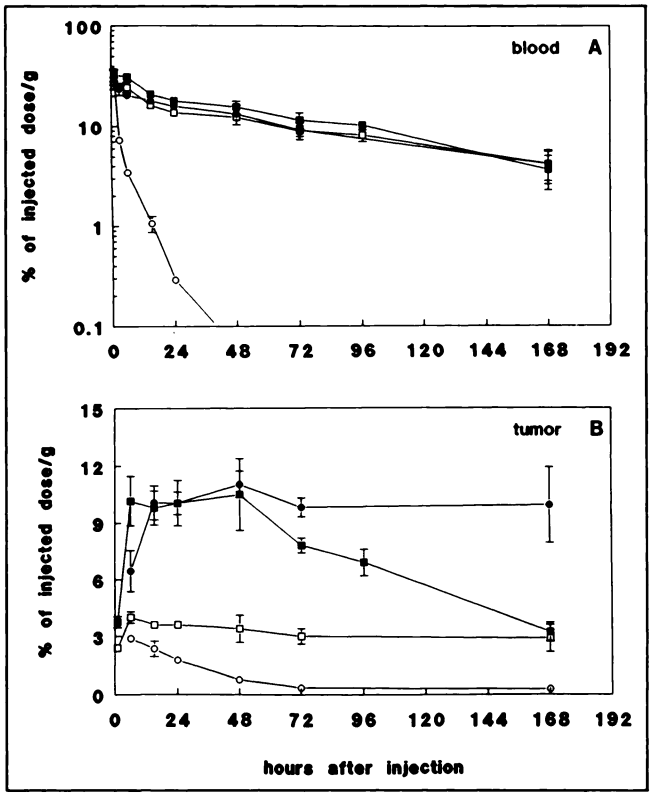

FIGURE 1. Pharmacokinetics in blood (A) and tumor uptake (B) of radiolabeled Mabs in nude mice bearing IGROV1 xenografts. ● = c-MOv18 IgG; ○ = c-MOv18 $F(ab')_2$; ■ = m-MOv18 IgG; □ = control Mab IgG. Vertical bars indicate s.d. Note: ordinates show different scales.

respectively, but for c-MOv18 $F(ab')_2$ fragments no retention was observed. The control IgG showed a maximum uptake in the tumor of 4.5%ID/g at 6 hr after injection without retention.

For m-MOv18 IgG, c-MOv18 IgG and c-MOv18-$F(ab')_2$ uptake in normal tissues was much lower than in tumors. At 72 hr after injection, liver uptake for the IgGs was 2.1%ID/g. For c-MOv18 $F(ab')_2$, 0.5%ID/g was measured in the liver at 6 hr after injection. Other tissues showed an equal or a lower uptake than that in the liver. An exception to the normal organ distribution pattern was the uptake of $F(ab')_2$ fragments in the kidneys which was as high as 47.2%ID/g at 1 hr after injection. This percentage decreased to 9.0, 4.5 and 0.9 at 3, 6 and 15 hr, respectively, after injection.

Tumor-to-nontumor (T/NT) ratios for c-MOv18 IgG were slightly higher than for m-MOv18 IgG both 72 hr and 168 hr after injection (Table 1). T/NT ratios varied largely for IgGs and $F(ab')_2$ fragments. For the $F(ab')_2$ fragments of c-MOv18, the tumor/blood ratios were approximately sixfold higher than for c-MOv18 IgG. Also, tumor-to-normal organ ratios were more favorable for $F(ab')_2$ fragments than for IgG, with the exception of the tumor-to-kidney ratio.

A biodistribution experiment with radiolabeled m-

TABLE 1
Tumor-to-Nontumor Ratios After Intravenous Injection of a Tracer Dose of Various Forms of Radiolabeled Mab MOv18 in IGROV1-Bearing Nude Mice

	m-MOv18 IgG		c-MOv18 IgG		c-MOv18 F(ab')$_2$	
Time*	72	168	72	168	24	48
Blood	0.7	0.9	1.1	1.8	6.2	11.6
Liver	3.8	3.9	6.7	11.0	20.7	20.0
Spleen	5.5	6.0	8.7	11.2	29.4	32.4
Heart	3.1	3.3	7.1	8.2	23.1	39.8
Kidney	4.0	4.5	7.9	8.8	5.3	15.3
Intestine	8.1	9.0	11.7	16.4	35.4	55.0
Muscle	9.6	9.7	19.8	18.5	59.8	122.1
Femur	6.5	8.0	12.9	12.4	21.3	73.3

* Hr after injection.

MOv18 IgG was carried out in mice bearing WiDr colon cancer xenografts which did not express the relevant antigen. The blood half-life of ^{125}I-m-MOv18 IgG was 80 hr. Tumor uptake was 5%ID/g at 24 hr (Fig. 2) and was in the same range as that of the control IgG 2C7 in IGROV1 xenografts.

Dosimetry

Radiation dose measurements in blood, tumors and normal tissues were derived from the data of the biodistribution experiments (Table 2). The radiation absorbed dose in IGROV1 xenografts delivered by 10 μCi radiolabeled m-MOv18 IgG and c-MOv18 IgG measured 39 cGy and 49 cGy, respectively. Doses to the blood exceeded those to the tumors, while normal organs received more than threefold lower doses. For c-MOv18 F(ab')$_2$ fragments, the tumor radiation absorbed dose was only 5 cGy, but it was higher than that for the blood and normal tissues. The kidneys of mice injected with the c-MOv18 F(ab')$_2$ fragments received a relatively high dose of 5.4 cGy.

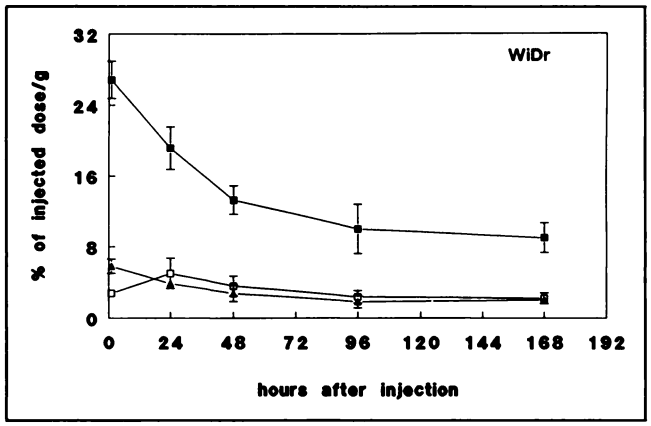

FIGURE 2. Pharmacokinetics of ^{125}I-m-MOv18 IgG in blood (■), tumors (□) and liver (▲) of nude mice bearing WiDr colon cancer xenografts that do not express the MOv18 antigen. Vertical bars indicate s.d. Note: scale differs from Figure 1.

TABLE 2
Dosimetry of Radiolabeled Mabs in IGROV1-Bearing Mice

	m-MOv18 IgG*	c-MOv18 IgG*	c-MOv18 F(ab')$_2$*	Control 2C7 IgG*
Tumor	39	49	5.0	19
Blood	69	60	4.0	65
Liver	12	10	0.9	12
Spleen	10	8	0.7	9
Heart	17	11	1.1	15
Kidney	13	9	5.4	12
Intestine	6	5	0.7	6
Muscle	4	3	0.2	3
Femur	7	7	0.5	6

* Radiation absorbed doses in cGy/10 μCi injected dose calculated over 0–168 hr.

Patient Study

No adverse reactions were noted after i.v. administration of the radiolabeled Mabs. Figure 3 is a planar immunoscintigram of the posterior abdomen showing the distribution of Mab c-MOv18 IgG labeled with ^{123}I. Especially at 24 hr, two areas of high activity were detectable in the pelvic region, corresponding with both tumorous ovaries. At all time points, uptake in the circulation was clearly visible. Other areas of high activity were observed at the site of normal organs, such as kidneys, spleen and liver. For comparison, magnetic resonance imaging (MRI) had been performed 10 days before surgery (Fig. 4). Two tumor lesions with high density were clearly visible in the pelvic region.

The uptake data for tumor and normal tissues of the patient is shown in Table 3. The mean uptake of ^{125}I-c-MOv18 IgG in the tumorous ovaries was 12.2×10^{-3} %ID/g (range: 9.0–15.4). For ^{131}I-c-MOv18 F(ab')$_2$ fragments, the mean uptake was 2.7×10^{-3} %ID/g (range: 1.8–3.6). The mean uptake of radiolabeled c-MOv18 IgG and c-MOv18 F(ab')$_2$ in the peritoneal metastases (including the omental metastases) was 3.2×10^{-3} %ID/g (range: 1.1–4.3) and 0.7×10^{-3} %ID/g (range: 0.3–1.2), respectively. For the uptake in normal tissue, the mean %ID/g in fat, muscle, peritoneum and skin were used. The tumor (ovaries) to normal tissue ratios were 11.1 and 10.8 for IgG and F(ab')$_2$ fragments, respectively. The tumor (ovaries)-to-blood ratios were 2.7 and 6.8, respectively. The clearance of c-MOv18 as IgG showed a half-life of 52 hr. The alpha and beta half-lives for the F(ab')$_2$ fragments were 1.3 hr and 14.1 hr, respectively.

At microscopy, the tumor was diagnosed as a poorly differentiated serous adenocarcinoma of the ovary with multiple peritoneal metastases. Tumor tissue was positive with Mab MOv18. The extent of the disease corresponded with FIGO Stage III.

DISCUSSION

We have analyzed the chimeric Mab MOv18, consisting of the variable regions of the murine Mab MOv18 and the

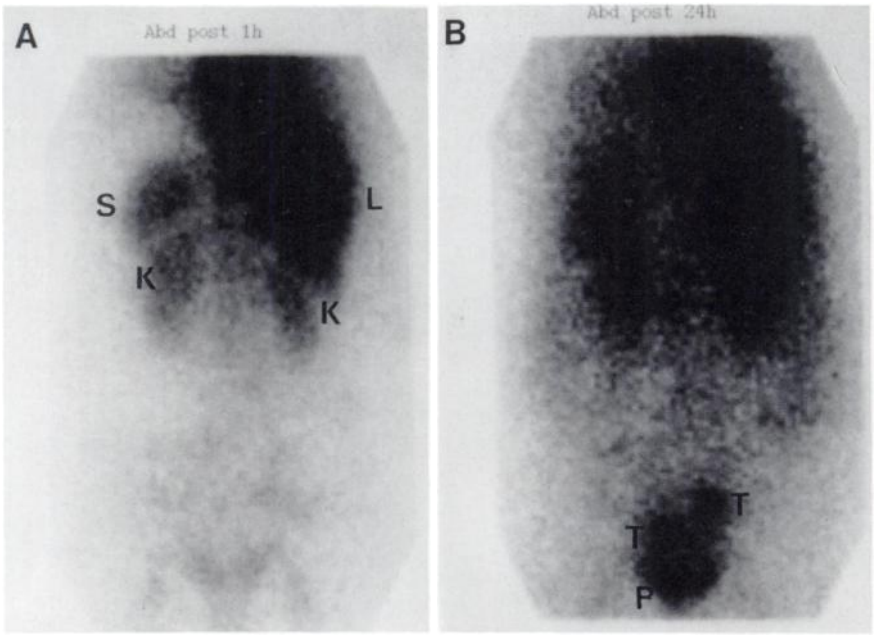

FIGURE 3. Planar posterior immunoscintigrams (^{123}I activity) of a patient suspected of having ovarian cancer, 1 hr and 24 hr after i.v. injection of a combination of ^{123}I-c-MOv18 IgG, ^{125}I-c-MOv18 IgG and ^{131}I-c-MOv18 F(ab')$_2$ fragments. Especially at 24 hr after injection, areas of high activity are visualized in the pelvic region and at the right side of the abdomen. Nonspecific uptake can be observed in the liver, the spleen, the kidneys and the bladder. The uptake in the blood decreased with time. T: tumor; L, liver; S: spleen; K: kidney; B: bladder.

constant human IgG1 regions, for its in vitro characteristics and in vivo behavior in ovarian cancer bearing nude mice and in an ovarian cancer patient. No differences were observed between m-MOv18, c-MOv18 IgG and c-MOv18 F(ab')$_2$ fragments in binding to IGROV1 cells expressing the relevant antigen. The affinity constants of c-MOv18 as IgG and F(ab')$_2$ of 5.2×10^9 M^{-1} and 5.8×10^9 M^{-1}, respectively, were slightly higher than those reported for m-MOv18 IgG by Miotti et al. (*9*), who obtained an affinity between 2–11 $\times 10^8$ M^{-1} using OVCAR-3 cells. In nude mice bearing IGROV1 xenografts, specific tumor uptake was shown to be similar for the murine and the chimeric IgG. Uptake of c-MOv18 F(ab')$_2$ fragments in IGROV1 xenografts was threefold lower than that of c-MOv18 IgG, but tumor-to-blood ratios were sixfold higher. Tumor lesions in an ovarian cancer patient could clearly be visualized with radiolabeled c-MOv18, and preferential tumor uptake of both iodinated c-MOv18 IgG and c-MOv18 F(ab')$_2$ fragments could be demonstrated. On the basis of our study, c-MOv18 seems a good candidate for evaluation in ovarian cancer patients.

The similar distribution of chimeric and murine Mab MOv18 IgG in a relevant human tumor model observed in our study confirms the observations of Saga et al. (*23*) for an anti-CALLA Mab, of Mueller et al. (*24*) using an anti-GD2 antibody and of Colcher et al. (*25*) for Mab B72.3. F(ab')$_2$ or Fab fragments of chimeric Mabs have not been investigated in these studies. The maximum %ID/g tumor tissue appeared remarkably similar for all these antibodies in experimental tumors in mice. The

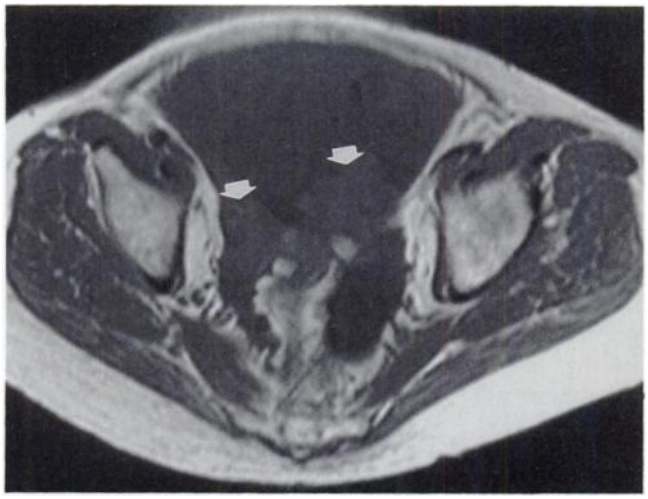

FIGURE 4. Transversal magnetic resonance imaging (MRI), T1 weighed through the pelvic region at 10 days before surgery (Teslacon II, General Electric). Arrows indicate high density areas in the pelvic region corresponding with ovaries replaced by tumor tissue.

TABLE 3
Uptake of Radioactivity at 48 Hr After Intravenous Administration of a Tracer Dose of ^{125}I-c-MOv18 IgG Plus ^{131}I-c-MOv18 F(ab')$_2$ Fragments in an Ovarian Cancer Patient

Tissue	n	^{125}I-MOv18 IgG $\times 10^{-3}$ %ID/g	^{131}I-MOv18 F(ab')$_2$ $\times 10^{-3}$ %ID/g
Tumor Tissue			
Ovary	2	12.2	2.7
Malignant ascites	1	4.8	1.6
Omentum	1	4.3	1.2
Peritoneal metastases	3	2.8	0.5
Normal Tissue			
Peritoneum	1	2.1	0.4
Skin	1	1.3	0.3
Muscle	1	0.7	0.2
Fat	1	0.3	0.1
Blood	1	4.5	0.4

overall clearance from the blood of radiolabeled m-MOv18 IgG was somewhat slower than that of c-MOv18 IgG, which was also shown for m-B72.3 versus c-B72.3 in the LS174T colon cancer model (*25*). With the exception of the fragments, the radiation doses to the blood exceeded those to the tumor in the first week after injection. If future radioimmunotherapy with c-MOv18 IgG will be considered in patients, it may be anticipated that myelosuppression is the dose-limiting factor. However, the relationship between the radiation dose to the blood and the extent of bone marrow damage is still unclear.

Recently, immunoscintigraphic results with ^{131}I-labeled murine Mab MOv18 in ovarian cancer patients have been reported (*13*). Especially for tumors in the pelvic region, a high sensitivity (90%) was achieved, without false-positive results. After i.v. injection, the radiolabeled m-MOv18 IgG showed a blood alpha half-life of 4.2 hr and beta half-life of 66.9 hr. A tumor-to-background ratio of 1.9–2.8 was determined with the region of interest technique of serial immunoscintigrams. In our patient, we demonstrated tumor localization by external scanning. We also determined the actual amount of radioactivity in the various biopsies obtained at surgery and calculated a mean tumor-to-normal tissue ratio of 11 for c-MOv18 IgG. No difference in tumor-to-normal tissue ratios was observed between IgG and F(ab')$_2$ fragments in contrast to our findings in the IGROV1 tumor model. The explanation for this discrepancy may be found in the relatively higher uptake of c-MOv18 in normal tissues of the patient compared with that in mice. The clearance from the blood of c-MOv18 IgG in our patient was slightly faster than that reported for m-MOv18 (*13*). Because of the relatively rapid clearance rate of c-MOv18 IgG compared with that of other chimeric Mabs, such as c-17-1A (*6–8*), and the good tumor-localizing properties, a favorable therapeutic index of c-MOv18 may be expected. Furthermore, patients investigated with c-MOv18 will have, in all probability, a lower risk of developing human anti-mouse antibodies upon multiple injections. Thus, chimeric Mab MOv18 can be a possible alternative for radioimmunotherapy.

Our study comparing m- and c-MOv18 Mab showed similar binding characteristics, high uptake in tumor tissue of ovarian cancer bearing nude mice and good tumor localization in a patient with ovarian cancer. The clinical study will be extended to further explore the immunogenicity of c-MOv18, its pharmacokinetics, tumor-localizing capacity, the tumor versus normal tissue uptake and whether whole IgG or smaller fragments will be most suitable for radioimmunotherapy of ovarian cancer.

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