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Radioimmunoscintigraphy of Ovarian Cancer with the MOv18 Monoclonal Antibody

F. Crippa, G.L. Buraggi, E. Di Re, M. Gasparini, E. Seregni, S. Canevari, M. Gadina, M. Presti, A. Marini and E. Seccamani

The monoclonal antibody (Mab) ^{131}I-MOv18 was administered to 30 patients with ovarian carcinoma intravenously (n = 20) and intraperitoneally (n = 10). After intraperitoneal administration, higher tumour uptake (mean values 1.3% vs. 0.8%) and a better tumour/background ratio (mean values 2.8 vs. 1.9) than after intravenous injection were obtained. Moreover, after intraperitoneal administration the uptake in non-affected organs, such as liver and spleen, was lower. However, occasionally the favourable results of the intraperitoneal route were cancelled by persistent pelvic non-specific accumulations of ^{131}I-MOv18. The possibility to change the biodistribution pattern in the latter cases with peritoneal washing was evaluated. 3 patients were submitted to this procedure and an improvement in the radiotracer biodistribution was obtained in 1 case. With regard to tumour detection, the average sensitivity (73%) showed a significant difference from the sensitivities for abdominal (61%) and pelvic lesions (90%). No false positive results were noted.
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INTRODUCTION

OVER the past 10 years, radioimmunoscintigraphy (RIS) has been proposed for the imaging of several primary and secondary human tumours [1]. As far as the clinical applications of radiolabelled monoclonal antibodies (Mab) are concerned, ovarian carcinoma has been one of the tumours most highly investigated with RIS [2–17]. The aggressive biological behaviour of this tumour still makes its management difficult, and in order to overcome this problem, significant improvements, both in the diagnosis of the disease and in its therapy [18, 19] are of fundamental importance. However, more than 75% of patients with ovarian carcinomas have their disease apparently confined to the peritoneal cavity [20]. Therefore RIS of ovarian cancer has been performed using two different routes of administration of the radiolabelled Mab: intravenous [2–12, 14, 16, 17] and intraperitoneal [10, 12, 13, 15].

In the past years we have selected and characterised numerous murine Mabs against ovarian cancer. One of them, MOv18, exhibited a very restricted pattern of tissue distribution [21] and a good stability on the cell membrane of the target antigen [22]. Moreover, very promising results were obtained both in a preclinical study [23] and in a preliminary clinical study [12]. Therefore, we planned a clinical trial in patients affected by advanced ovarian carcinomas with a scheduled surgery within the next 15 days. The Mab, radiolabelled with ^{131}I, was administered intravenously or intraperitoneally. The objective of this study was to investigate both the feasibility of RIS in ovarian cancer with MOv18 Mab and the possibility to obtain a biologically suitable biodistribution for further therapeutic applications.

Correspondence to G.L. Buraggi.
F. Crippa, G.L. Buraggi, M. Gasparini and E. Seregni are at the Division of Nuclear Medicine; E. Di Re is at the Division of Gynaecologic Oncology; S. Canevari and M. Gadina are at the Division of Experimental Oncology E, Istituto Nazionale Tumori, Via Venezian 1, 20113 Milan; M. Presti and A. Marini are at the III Gynaecologic Obstetric Clinic, University of Milan, Milan; and E. Seccamani is at the Sorin Biomedica, Saluggia, Italy.
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MATERIALS AND METHODS

Monoclonal antibody MOv18

The characteristics of the MOv18 Mab have been described in detail elsewhere [21]. Briefly, it is a murine IgGlk which recognises a 38 kD glycoprotein expressed on the cell membrane of about 90% of human ovarian carcinomas. For human use MOv18 was purified, tested for sterility and absence of pyrogenicity and radiolabelled with ^{131}I (IODO-GEN method) by Sorin Biomedica (Saluggia, Italy) to a final specific activity ranging from 92 to 228 MBq/mg. To verify the maintenance of binding activity and specificity after radiolabelling, direct solid-phase radioimmunoassay (RIA) on cells expressing the relevant antigen was carried out as described elsewhere [21]. The immunoreactive fraction of the radiolabelled Mab, determined by a cell-binding assay carried out at infinite antigen excess [24], was tested for each lot of reagent and was found be, on average, 40%.

Patients

30 patients (mean age, 53 years; range, 27–69) entered this study after informed consent was obtained. They were affected by histologically confirmed advanced primary or relapsed ovarian carcinoma. Tables 1 and 2 summarise their principal characteristics. Each patient, under blocked thyroid conditions, was administered with a different lot of ^{131}I-MOv18 3 days after the labelling procedure. In a group of 20 patients ^{131}I-MOv18 was administered by intravenous injection. Each patient received a mean dose of 0.58 mg of MOv18 (range 0.25–1.20) corresponding to 103 MBq of ^{131}I (range 63–166). In a second group of 10 patients, a catheter was introduced under local anaesthesia into the peritoneal cavity and after the abdominal perfusion with albumin-macroaggregates labelled with ^{99m}Tc and washed with 500 ml of normal saline was checked, ^{131}I-MOv18 was infused in 500–1500 ml of normal saline according to the presence or absence of ascitic fluid. The mean administered quantity of

Table 1. Principal characteristics of ovarian carcinoma patients submitted to intravenous administration of ^{131}I-MOv18

Patient	Histological type	Stage*	^{131}I (MBq)	Mab (mg)	Surgery	Disease status†
1	Serous	III	81	0.43	Laparotomy	RD < 1 cm
2	Serous	III	71	0.43	Laparotomy	RD < 1 cm
3	Serous	III	64	0.25	Laparotomy	RD < 1 cm
4	Serous	IV	68	0.25	Laparotomy	RD < 5 cm
5	Serous	III	63	0.48	Laparotomy	RD > 10 cm
6	Serous	III	108	0.48	Debulking	BD
7	Serous	IV	83	0.44	Debulking	BD
8	Serous	III	78	0.41	Debulking	BD
9	Serous	III	112	0.70	Debulking	BD
10	Serous	III	65	0.56	Debulking	BD
11	Serous	III	134	0.75	Laparotomy	RD < 5 cm
12	Serous	III	138	1.00	Debulking	BD
13	Serous	III	166	1.28	Debulking	BD (ascites)
14	Serous	III	121	0.50	Laparotomy	RD < 10 cm
15	Serous	III	126	0.65	Laparotomy	RD < 2 cm
16	Mixed	III	145	0.52	Laparotomy	RD < 1 cm
17	Mixed	III	76	0.33	Laparotomy	RD > 10 cm
18	Mixed	III	142	0.53	Debulking	BD
19	Undiff.	III	73	0.44	Laparotomy	RD > 10 cm
20	Endomet.	III	157	1.21	Debulking	BD (ascites)

*Figo classification. †After surgery.
Debulking = primary debulking surgery, laparotomy = second look laparotomy, undiff. = undifferentiated, endomet. = endometrial.
RD = residual disease, BD = bulky disease.

MOv18 was 0.64 mg (range 0.30–1.26) corresponding to 114 MBq of ^{131}I (range 52–186). 3 patients with persistent pelvic non-specific accumulations of the radiotracer were submitted to peritoneal washing 72 h after Mab administration. They were intracavitarily infused with 2000 ml of normal saline solution which was recovered 30 min later after active movements of the patients. Patients underwent laparatomy within 15 days after RIS either as a debulking primary surgery (12 patients) or second- or third-look surgery to assess the disease status (18 patients).

Pharmacokinetic analysis

The pharmacokinetic blood behaviour of ^{131}I-MOv18 was studied in 12 (see Table 3 for identification) of the 30 patients

Table 2. Principal characteristics of ovarian carcinoma patients submitted to intraperitoneal administration of ^{131}I-MOv18

Patient	Histological type	Stage	^{131}I (MBq)	Mab (mg)	Surgery	Disease status
21	Serous	III	71	0.30	Laparotomy	RD < 1 cm
22	Serous	IV	52	0.30	Laparotomy	RD < 1 cm
23	Serous	III	186	1.20	Debulking	BD (ascites)
24	Serous	III	108	0.58	Laparotomy	RD < 5 cm
25	Serous	III	111	0.61	Laparotomy	RD < 1 cm
26	Serous	III	109	0.85	Debulking	BD
27	Serous	III	88	0.96	Laparotomy	RD < 1 cm
28	Serous	III	138	0.98	Laparotomy	RD < 1 cm
29	Mixed	III	144	0.69	Laparotomy	RD < 2 cm
20	Mixed	III	127	0.66	Debulking	BD (ascites)

Table 3. Blood pharmacokinetics of ^{131}I-MOv18 evaluated in 12 patients with ovarian cancer

Patient	Route of administration	$t_{\frac{1}{2}}$ (h) Alpha phase	$t_{\frac{1}{2}}$ (h) Beta phase
1	Intravenous	1.5	165
2	Intravenous	7.5	101.7
3	Intravenous	2.3	39.1
4	Intravenous	3.4	40.6
6	Intravenous	8.2	76.9
10	Intravenous	5.6	72.5
13	Intravenous	1.7	63.2
14	Intravenous	2.3	31.5
16	Intravenous	8.7	40.9
17	Intravenous	0.7	37.9
27	Intraperitoneal	—	273.5
28	Intraperitoneal	—	147.0

who underwent scintigraphic examination. Only 2 of these patients received intraperitoneal administration of the radiotracer, whereas 10 patients were injected intravenously. The pharmacokinetic analysis was performed by collecting blood samples at 1 h, 3 h, 24 h and then at 24-h intervals for 4–8 days after the ^{131}I-MOv18 administration. Since the radioactivity which bound to the red blood cells was shown to be irrelevant upon clotting, the samples were centrifuged and the serum was recovered. An aliquot from each serum sample was counted in a gamma counter against a standard of the injected dose. For each serum sample the protein bound radioactivity was measured by paper chromatography in 10% trichloroacetic acid (TCA). The serum clearance of ^{131}I-MOv18 was assessed by plotting the molarity of the Mab against the time in a semilogarithmic plot. The molarity of the Mab was calculated from the counts after the physical decay correction by knowing the volumes of the serum samples and by taking into account the percentage of TCA precipitable activity, the specific activity and the efficiency of the instrument used. The distribution half-lives ($t_{\frac{1}{2}}\alpha$) were only calculated in the intravenous administered patients, whereas the terminal phase half-lives ($t_{\frac{1}{2}}\beta$) were calculated for all patients. The data in both the alpha and beta components were extrapolated from the clearance curves using the method described by Mayerson and Gibaldi [25]. The patient sera were run on 10% sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), and autoradiography performed on these gels, using image-intensifying screens at −70°C, showed the presence of radioactivity on a single species for up to 30 min with a molecular mass similar to that of MOv18. This was no longer visible after 24 h.

Radioimmunoscintigraphic examination

In each patient, 1, 3 and 24 h after radiotracer administration and then at 24-h intervals for 4–8 days, analogue and digital scintigraphic maps of the whole-body and regional Mab biodistribution were recorded using a large-field gamma-camera (Selo KR7) interfaced with a computer (Digital PDP-11). Evaluation of the whole body clearance and organ kinetics of ^{131}I-MOv18 was performed in 10 and 6 patients injected respectively intravenously and intraperitoneally by using the region of interest technique on the serial maps. To evaluate the diagnostic sensitivity and specificity in tumour detection, the RIS results were compared to the surgical reports of the patients.

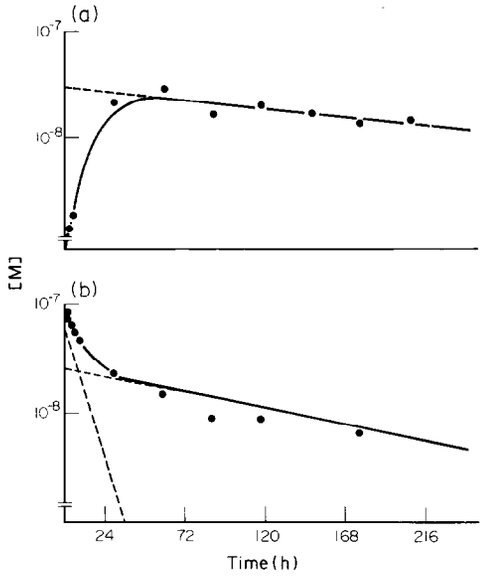

Fig. 1. Blood clearance curves evaluated in patients nos 28 and 6, respectively, after ^{131}I-Mov18 intraperitoneal (a) or intravenous (b) administration. $t_{\frac{1}{2}}$ values are in Table 3.

RESULTS

With regard to the pharmacokinetic study, the analysis of the blood clearance curves indicated that the ^{131}I-MOv18 kinetics fits an open two compartment model. In Fig. 1 are reported as an example two blood clearance curves, after intraperitoneal (patient no. 28) and intravenous (patient no. 6) administration. Table 3 shows the calculated values of $t_{\frac{1}{2}}\alpha$ and $t_{\frac{1}{2}}\beta$ for all 12 patients who underwent blood pharmacokinetic evaluation. On average, the $t_{\frac{1}{2}}\alpha$ and $t_{\frac{1}{2}}\beta$ respectively were 4.2 h (S.D. 2.9) and 74.9 h (41.9). Both parameters exhibited a wide range of variability and no correlation could be found between the short and terminal phase lengths. Since each patient was administered with a different lot of ^{131}I-MOv18, in order to determine the influence of the specific activity of the administered radiotracer on the lengths of the alpha and beta phases, two separate regression analyses were performed. In both cases no significative correlation was found, however, an inverse correlation between the beta phase and specific activity of the radiotracer was observed ($r = -0.45, P < 0.145$). Even when evaluated in only 2 patients, the terminal half-life of the Mab in blood seemed to be longer after intraperitoneal administration. To confirm this observation and to further evaluate the pharmacokinetics of the radiolabelled Mab, the whole body disappearance and the percent uptake of ^{131}I-MOv18 in tumoral lesions and in selected non-affected organs (liver, spleen, heart) were calculated at different time. Figures 2A and 2B show, respectively, the mean disappearance curves of ^{131}I-MOv18 observed after intravenous and intraperitoneal administration. They were obtained considering for each organ 10 cases among patients who underwent intravenous administration and 6 cases among those receiving intraperitoneal administration (see legends for patients' identification). As regards the evaluation of regional uptake after intraperitoneal administration, it should be considered that it was sometimes difficult to determine the regional uptake during the first 24 h following administration when almost all of the radioactivity was present in the whole abdomen. The disappearance from the whole body was slower after intraperitoneal injection: in fact 20% of the injected dose was still present after about 96 h compared to 10% after intravenous administration. In spite of a higher percentage of remaining radioactivity in the whole body, the uptake from organs such as liver, spleen and

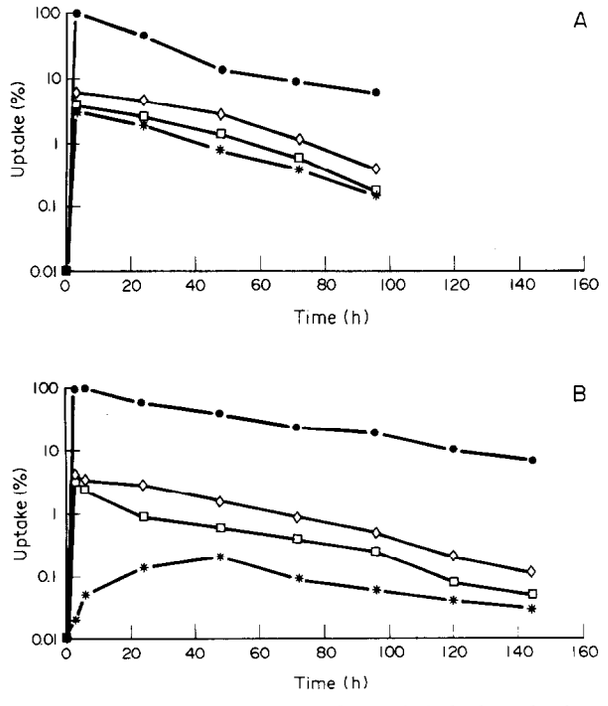

Fig. 2. Mean disappearance curves from whole body and selected organs (liver, heart, spleen) after administration of the radiotracer intravenously (panel A, patients 1, 2, 3, 5, 6, 12, 16, 18, 19, 20) or intraperitoneally (panel B, patients 21, 22, 23, 24, 28, 30) route. —●— whole body, —◇— liver, —*— heart, —□— spleen.

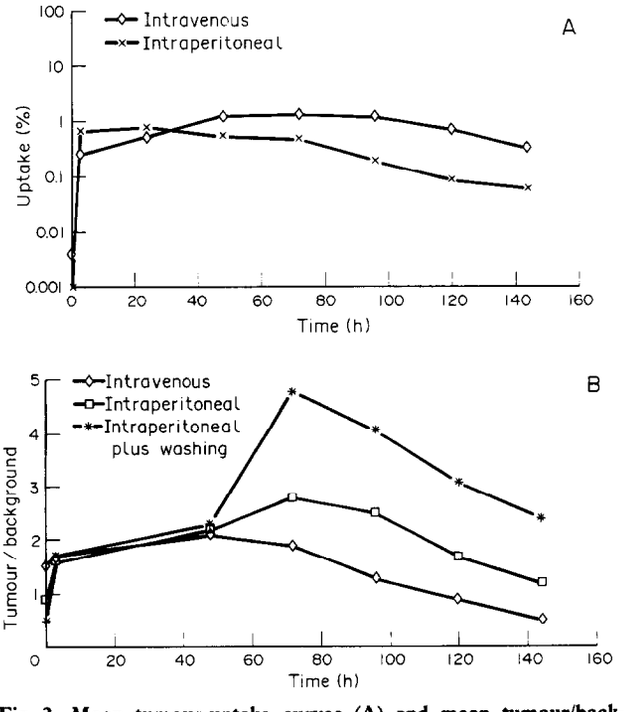

Fig. 3. Mean tumour-uptake curves (A) and mean tumour/background ratio curves (B) after intravenous (14 patients) and intraperitoneal (6 patients) administration. For patient identification see Fig. 4. Peritoneal washing curve concerns the case illustrated in Fig. 5.

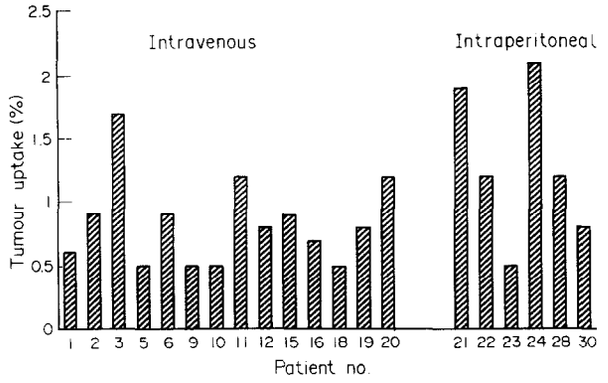

Fig. 4. Highest tumour uptake of ^{131}I-MOv18 in 14 patients after intravenous injection and in 6 patients after intraperitoneal infusion of the radiotracer.

heart, generally characterised by a high non-specific uptake [10], was lower after intraperitoneal administration. The trends of the tumour uptake and of the tumour/background ratio were evaluated in 14 patients injected intravenously and 6 patients infused by the intraperitoneal route and the results are shown as means, respectively, in Figs 3A and 3B. The highest values of tumour uptake were reached 24–48 h after the intravenous administration and 48–72 h following the intraperitoneal injection and were more favourable after the intraperitoneal administration than after intravenous injection. The mean obtained values were significantly different (ANOVA, $P = 0.05$), being, respectively, 1.3% (S.D. 0.62; range 0.5–2.1%) and 0.8% (0.34; 0.5–1.7%). The mean tumour/background ratios calculated at the same times were 2.8 (range 1.6–5.2) after intraperitoneal administration and 2.1 (1.3–4.1) after intravenous injection. The highest values of tumour uptake relative to the patients of Fig. 3, irrespective of the tumour anatomical site and the time of analysis are shown in Fig. 4. 3 of the patients submitted to intracavitary administration showed a persistent non-specific activity of the radiotracer in the pelvic region. We tried to change this unfavourable biodistribution pattern by using peritoneal washings. An improvement of the tumour/background ratio (Fig. 3B) and a better localisation of the tumour lesion (Fig. 5) were obtained in only 1 of these cases, whereas in the other 2 the biodistribution patterns remained unchanged.

Table 4. Comparison between RIS results and tumour localizations detected by surgery

Site of lesion	No.	RIS positivity
Abdomen	44	27(61%)
Diaphragm	7	0
Liver	2	0
Gut	13	7
Nodes	4	2
Peritoneum	8	8
Omentum	10	10
Pelvis	31	28(90%)
Ovary	16	16
Peritoneum	13	11
Bladder	2	1
Total	75	55(73%)

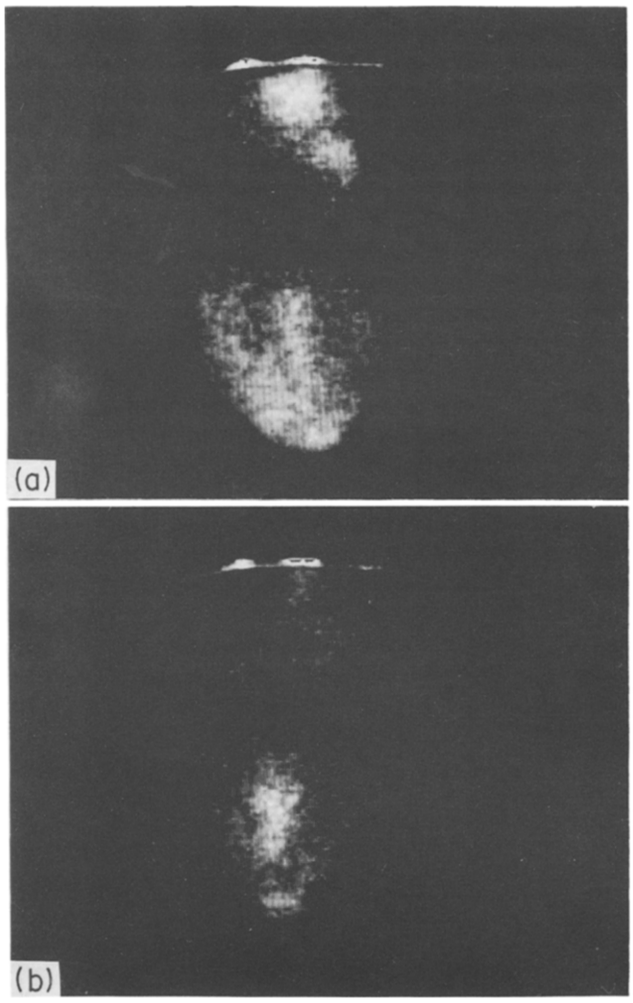

Fig. 5. Pelvic immunoscintigraphic maps (anterior view) obtained 72 h after intraperitoneal administration of ^{131}I-MOv18 in patient no. 27. The tumour lesion infiltrating the bowel, barely visible (a) due to a persistent non-specific accumulation of radiotracer in the pelvis, became evident (b) after peritoneal washing.

In regard to tumour detection, the results of RIS were compared to those obtained in the surgical evaluation of the patients. Since no difference was observed between the two routes of administration, the data reported in Table 4 refer to either one. In these patients 75 tumour localisations were determined by laparatomy. Of these, 55 were detected by RIS (73%). Considering their anatomical sites, a significant difference in the diagnostic sensitivity of RIS between the abdomen and pelvis was evident. In fact, the positivity rate of RIS was 28/31 (90%) in the pelvis whereas in the abdomen 27/44 (61%) lesions were detected. This difference was due to the unsuccessful detection of the lesions located in the upper abdomen (15 lesions, all with negative RIS). The small number of upper abdominal lesions in patients with intraperitoneal administration (3 out of the total 15 lesions) precluded any further evaluation of sensitivity.

DISCUSSION

Several clinical studies with radiolabelled Mabs have pointed out that the major limitation of RIS was the low target to non-target ratio mainly due to the relatively long persistence in the blood pool of the currently used radiotracers [10]. Moreover, in a previous prospective study with the Mab ^{131}I-OC125 injected intravenously in a selected group of ovarian carcinoma patients, we showed that a further limitation was represented by the poor

sensitivity in detection of lesions localised in the upper abdomen [17]. A more favourable biodistribution of radiolabelled Mabs and a significant increase in the tumour/non-tumour ratio by intracavitary administration has been reported [10, 13, 15, 26]. Therefore, we selected a new Mab, MOv18, to be exploited for RIS in ovarian cancer and we compared its pharmacokinetics, biodistribution and tumour detection after intravenous and intraperitoneal routes of administration. Since the study was aimed to evaluate the possibility of a further MOv18 therapeutic application the whole immunoglobulin labelled with ^{131}I was used.

In agreement with previous studies [27–29], the blood pharmacokinetic evaluation of ^{131}I-MOv18 showed, on average, fairly long terminal phase half-lives but a wide intrapatient variability, probably attributable to the different status of the disease. Although only 2 patients were examined after intraperitoneal administration, the $t_{\frac{1}{2}}\beta$ seemed longer than after intravenous injection. This observation was confirmed by the whole-body disappearance curves. Noteworthy was the obtained inverse correlation between $t_{\frac{1}{2}}\beta$ of the Mab and a greater number of iodine per molecule. Even though this correlation was not statistically significant, due to individual variability, it deserves further investigation, and emphasises the importance of the stability of the radiotracer which might affect its biological behaviour. Moreover the intraperitoneal administration allowed to obtain a more favourable biodistribution of ^{131}I-MOv18 than with the intravenous route. In fact, the intracavitary infusion of the Mab was characterised by a lower non-specific uptake in non-affected organs, by a higher tumour uptake and a better tumour/background ratio.

As regards tumour detection, we obtained a high value of the overall diagnostic sensitivity (73%) and a very high specificity (100%), but no significant difference between the two routes of administration. These values, similar or even better than those previously reported, indicate that MOv18 represents an interesting Mab for the RIS of ovarian cancer and a prospective study aimed to confirm its diagnostic contribution is now in progress. For this type of clinical application we could expect significant improvements in the results by the use of antibody fragments labelled with other radionuclides with more favourable physical characteristics. However, in keeping with our previous experience with the Mab ^{131}I-OC125 [17], the present study reported a different sensitivity for the abdominal and pelvic tumour lesions (respectively, 61% vs. 90%) due to the unsuccessful detection of upper-abdominal lesions. Moreover, in 3 out of 10 cases, after the intraperitoneal administration we observed in the pelvic region persistent non-specific accumulation of the radiotracer which made the diagnostic interpretation of the immunoscintigraphic maps difficult. This limit has been reported by other researchers [26]. With regard to this problem, Ward *et al.* [30], using peritoneal washings showed, in a preclinical study, an improvement of the biodistribution with consequent significant improvement in the tumour/background ratio and a reduction of the systemic exposure. Therefore, we tried to apply peritoneal washings to 3 patients with pelvic non-specific accumulation of ^{131}I-MOv18. The results of this procedure were only useful in 1 case, where we obtained an important improvement in the tumour/background ratio and a better immunoscintigrafic detection of the tumour lesion.

In conclusion we suggest that, for diagnostic application, the intraperitoneal route of administration is not very useful. It did not provide substantial advantages compared to the intravenous route, taking into account the more invasive procedure of intraperitoneal infusion and the requirement of peritoneal washings in about 30% of cases. However, the more favourable biodistribution obtained by intraperitoneal administration makes this route probably the more appropriate one in the case of therapeutic applications.

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Comparison of Continuous and Intermittent Bolus Infusions of Metoclopramide during 5-day Continuous Intravenous Infusion with Cisplatin

Kiyoshi Mori, Yoshikuni Saitou, Keigo Tominaga, Kohei Yokoi and Naoto Miyazawa

In order to decide the administration method of metoclopramide for prevention or control of chemotherapy-induced nausea and vomiting in multidrug chemotherapy, with cisplatin 5-day continuous intravenous infusion (25 mg/m²/day) for patients with advanced lung cancer, a randomised crossover study of intermittent bolus infusion (1 mg/kg, 30 min, every 8 h, days 1–5) and continuous infusion (3 mg/kg/24 h, 120 h) of metoclopramide was performed. Both regimens included methylprednisolone and diphenhydramine given concurrently. The acute and delayed antiemetic effects were examined. 21 cases could be evaluated. There were 6 and 10 cases ($P = 0.048$), respectively, of no nausea and no vomiting; 14 and 18 cases ($P = 0.048$), respectively, of no vomiting; and vomiting episodes were seen 27 and 9 times, respectively ($P = 0.042$). Thus, metoclopramide continuous infusion was significantly superior in antiemetic effect compared to bolus infusion. Neither method had any serious side-effects and both were safe.
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INTRODUCTION

MULTIDRUG CHEMOTHERAPY, especially with cisplatin, is commonly used in the treatment of advanced cancer. Many ways of administering this therapy have been developed. In some institutes, including our hospital, cisplatin 5-day continuous intravenous infusion (CI) is used and good results have been obtained [1].

Although cisplatin CI causes fewer problems with the digestive system and has less renal toxicity than bolus infusion, the problem of control and prevention of chemotherapy induced nausea and vomiting still remains. No studies have been reported of a comparison of antiemetic agent regimens in cisplatin 5-day CI. Metoclopramide is the most commonly used antiemetic agent [2] and two methods of administration have been reported: intermittent bolus infusion (BI) and CI [2–9]. In our study, we performed a randomised crossover study of continuous and intermittent infusion of metoclopramide in multidrug chemotherapy with cisplatin 5-day CI in order to decide which method is better, examining acute and delayed antiemetic efficacy and side-effects. We also analysed metoclopramide pharmacokinetics.

Correspondence to K. Mori.
The authors are at the Department of Thoracic Disease, Tochigi Cancer Center, 4-9-13, Yonan, Utsunomiya-shi, Tochigi-ken, 320 Japan.
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PATIENTS AND METHODS

Study population

Our subjects were 24 hospitalised patients with primary lung cancer receiving cisplatin alone or multidrug chemotherapy including cisplatin at the Department of Thoracic Disease of the Tochigi Cancer Center. Patients' characteristics are shown in Table 1.

Treatment regimens

Patients with non-small cell lung cancer received cisplatin alone (25 mg/m²/day, 5-day CI) or in combination with vindesine