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Eur J Cancer, Vol. 29A, No. 8, pp. 1105–1111, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Potential Contribution of ^{131}I-Labelled Monoclonal Anti-CEA Antibodies in the Treatment of Liver Metastases from Colorectal Carcinomas: Pretherapeutic Study with Dose Recovery in Resected Tissues

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20 patients with liver metastases from colorectal carcinoma undergoing laparotomy received 15–60 mg intravenously, either intact or fragments of, anti-carcinoembryonic antigen (anti-CEA) monoclonal antobodies labelled with 0.55–1.48 GBq (15–40 mCi) of ^{131}I, 3–8 days prior to operation. The uptake measured per gram of metastases ranged from 0.33 to 6.6 × 10^{-3}% of injected dose. Tumour to liver uptake ratios ranged from 2 to 33. The radiation dose, estimated in 6 patients (3 of each group), for an extrapolated dose of 3.7 GBq (100 mCi) of ^{131}I ranged from 0.3 to 0.8 Gy in normal liver or spleen (an acceptable estimate for bone marrow radiation dose) and from 3.4 to 8.2 Gy to the hepatic metastases, indicating that probably other therapeutic modalities should be associated with radioimmunotherapy.
Eur J Cancer, Vol. 29A, No. 8, pp. 1105–1111, 1993.

INTRODUCTION

THE THERAPEUTIC use of radiolabelled monoclonal anti-carcinoembryonic antigen (anti-CEA) antibodies (Mab) has been the subject of several experimental xenograft studies [1, 2]. Clinically, radiolabelled antitumour antibodies have been used in the treatment of hepatic carcinomas, melanomas and B cell lymphomas [3–5]. However, very few clinical radioimmunotherapy studies involving patients with metastatic colon carcinoma have been reported [6, 7]. For cancer therapy, the theoretical advantage of Mab labelled with medium to high energy beta-emitting radionuclides, over immunotoxins [8–10] or immunodrug conjugates [11] comprises particle penetration and damage into several cell layers around the targeted tumour cells, the so-called crossfire phenomen.

At the clinical level, anti-CEA Mab labelled with ^{123}I have been used to detect local recurrences or distant metastases from colorectal carcinomas by immunoscintigraphy. For radioimmunotherapy, anti-CEA Mab have only been used in a pilot trial, including 7 patients who each received 3.7–7.4 GBq (100–200 mCi) of ^{131}I-labelled Mab through the hepatic artery. There was no significant tumour response, despite evidence of excellent tumour localisation obtained by tomoscintigraphy [6].

The purpose of the present study was to analyse the biodistribution and specific uptake of ^{131}I-labelled Mab and fragments in liver metastases and normal tissues by scintigraphy and direct measurement. The study was carried out in clinical conditions simulating those of radioimmunotherapy. We also tried to estimate the absorbed radiation dose delivered to metastases and normal tissues, and extrapolate these values for potential radioimmunotherapy protocols.

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Revised 9 Nov. 1992; accepted 25 Nov. 1992.

MATERIALS AND METHODS

Monoclonal antibodies and F(ab')2 fragments

We used anti-CEA Mab 35 and B7-25 described by Buchegger *et al.* [1, 2] and Mab F6 from CIS-bio International (Gif-sur-Yvette, France) [12]. All three Mab have been clinically evaluated by diagnostic immunoscintigraphy and shown not to accumulate significantly in any normal tissues, when labelled with ^{131}I or ^{123}I [13]. Furthermore, they were shown not to cross react *in vitro* with NCA-55, NCA-95, biliary glycoproteins or human granulocytes. The three Mab were of IgG1 isotype. $F(ab')_2$ fragments were prepared by pepsin digestion as previously described [1, 2] and purified by filtration on a sephadex G150 column.

Patient selection

Patients with histologically proven liver metastases from colorectal cancer were eligible for this study if they were selected for liver surgery to resect the metastases or for placement of an intra-arterial catheter for locoregional chemotherapy. Patients were excluded from participation in cases of prior exposure to mouse protein, allergy to iodine, medullary insufficiency (platelets $< 100\,000/mm^3$, leucocytes $< 4000/mm^3$), or any contra-indication for laparotomy (cardiac, pulmonary or renal disease). No chemotherapy or radiation therapy within the preceding 3 months was allowed. Informed consent was obtained from all patients before participation in the study.

Infusion of radiolabelled antibodies

Lugol's solution was administered orally beginning 3 days before the Mab infusion and continued for 3 weeks. Thirty milligrams of antibody radiolabelled with 0.58–1.48 GBq (15–40 mCi) ^{131}I were intravenously injected during a period of 1 h by an automatic pump with a lead-shielded reservoir. This infusion preceded laparotomy by 3–8 days.

Dosimetric studies

Absorbed dose D(Gy) calculations were based on the MIRD equation, expressed when target and source volume are the same [14] and are given by:

$$\bar{D}(o..o) = \tilde{A}_o \sum \Delta_i f_i(o..o) \quad (a)$$

where $\bar{D}(o..o)$ is the mean absorbed dose, $\tilde{A}_o$ the cumulated activity, Δ_i the equilibrium dose constant and f_i the absorbed fraction for an organ o and an i type radiation.

Certain physical and biological data are required for this formula.

Physical data. For the decay of ^{131}I we took into account only the b_5^- (E_{max} = 606 keV) and g_9 (364 keV) emissions whose values of Δ_i are published in MIRD pamphlet no. 10 [15]. For non-penetrating radiation b_5^-, f_i was assumed to be equal to 1. In the case of penetrating radiation g_9, the value of f_i depends on geometrical considerations and was assumed to be equal to 0.05 [16] for our study. On this basis and assuming monoexponential decay of the uptake in the foci, the relation (a) becomes (b), and is very close to the one used by Israel *et al.* [17].

$$\underset{[Gy]}{\bar{D}_0} \; @ \; 42 \times 10^{-4} \underset{(kBq/g)}{C_0} \; \underset{(day)}{T_{eff}} \quad (b)$$

where C_0 is the initial radioactive concentration in kBq/g and T_{eff} is the effective half-life.

Biological data. The biological data were derived from single photon emission computed tomography (SPECT) acquisition and surgical sample counting. SPECT was performed once daily after antibody administration until surgery using the large field of view gamma camera (STARCAM 500A, General Electric, Milwaukee, U.S.A.). The camera was fitted with a specially designed high-energy collimator. On the reconstructed images, regions of interest (ROI) were manually drawn for tumour and some normal tissues such as liver and spleen. The number of counts present in the ROI was plotted against time to calculate effective clearance of Mab.

During laparotomy, when only biopsies were obtained because of non-resectable metastases, the latter were mapped and every biopsy specimen was identified for comparison with imaging results. If hepatic resection was performed, separate tumour tissue fragments were also obtained from each patient. Every tissue sample was weighed and counted in a calibrated automatic gamma counter (Pharmacia-LKB 1282 CompuGamma). The radioactive concentration to kBq/g was calculated for tumour and normal tissue and correlated with ROI counting. Necrosis was subsequently assessed histologically.

RESULTS

Patients' characteristics

20 patients were injected with 30 mg Mab anti-CEA labelled with 0.58–1.48 GBq (15–40 mCi) ^{131}I, 3–8 days before surgery. A further 2 patients received 60 mg of MAb. 10 patients received intact antibodies (group I) and 10 received $F(ab')_2$ fragments (group II).

The main characteristics of these two groups are summarised in Table 1. All patients had liver metastases from colorectal cancer confirmed by biopsy. CEA plasma levels are higher in group II (mean = 51.6 ng/ml) than in group I (mean = 28.6 ng/ml). No toxicity was observed, but 1 patient was excluded from the study due to a mild allergic reaction.

Table 1. Patients' characteristics

Patient No.	Primary site	Plasma CEA (ng/ml)	Surgery
Intact Mab			
1	Rectum	35	10 LM: Biopsies
2	Sigmoid	15	1 LM: Resection
3	Sigmoid	19	1 AM: Resection
4	Rectum	9	4 LM: Biopsies
5	Right colon	57	1 LM: Resection
6	Rectum	1.9	1 LM: Resection
7	Rectum	2.6	1 LM: Resection
8	Med. colon	67	1 LM: Resection
9	Rectum	12	1 LM: Resection
10	Sigmoid	75	10 LM: Biopsies
Fragment Mab			
1	Sigmoid	38	3 LM: Biopsies
2	Sigmoid	2	>5 LM: Biopsies
3	Rectum	15	1 LM: Resection
4	Sigmoid	184	1 LM: Resection
5	Sigmoid	116	3 LM: Resection
6	Sigmoid	5.5	>5 LM: Biopsies
7	Sigmoid	3	1 LM: Resection
8	Sigmoid	50	1 LM: Resection
9	Sigmoid	26	10 LM Biopsies
10	Right colon	23	2 LM: Resection

LM, Liver metastases; AM, adrenal metastasis.

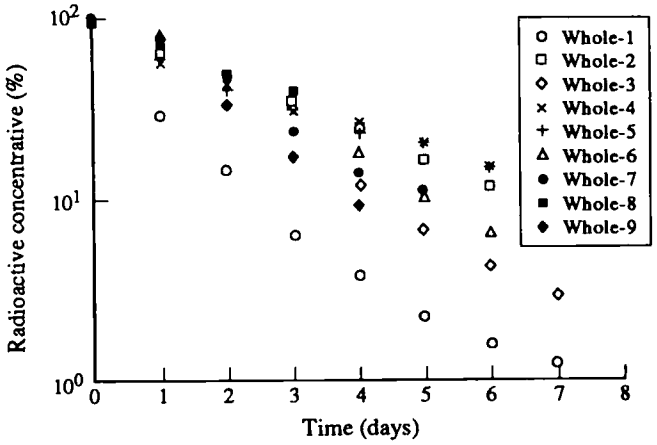

Fig. 1. Blood radioactive decay against time in 9 patients normalised to 100% at the day of injection (Whole-*n* means patient number *n* injected with intact Mab.

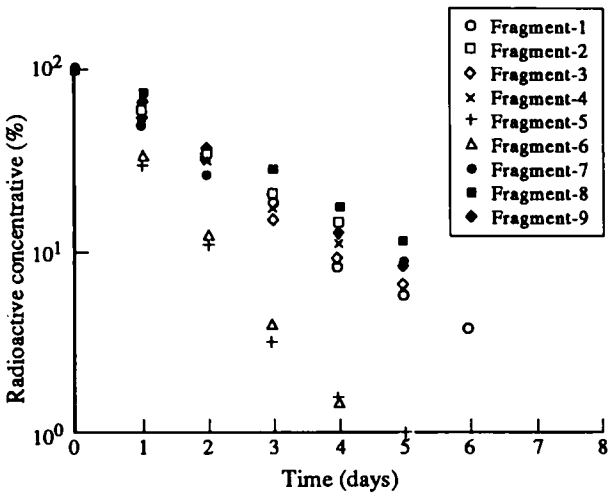

Fig. 2. Blood radioactive decay against time in 9 patients normalised to 100% at the day of injection (Fragment-*n* means patient number *n* injected with $F(ab')_2$ fragments).

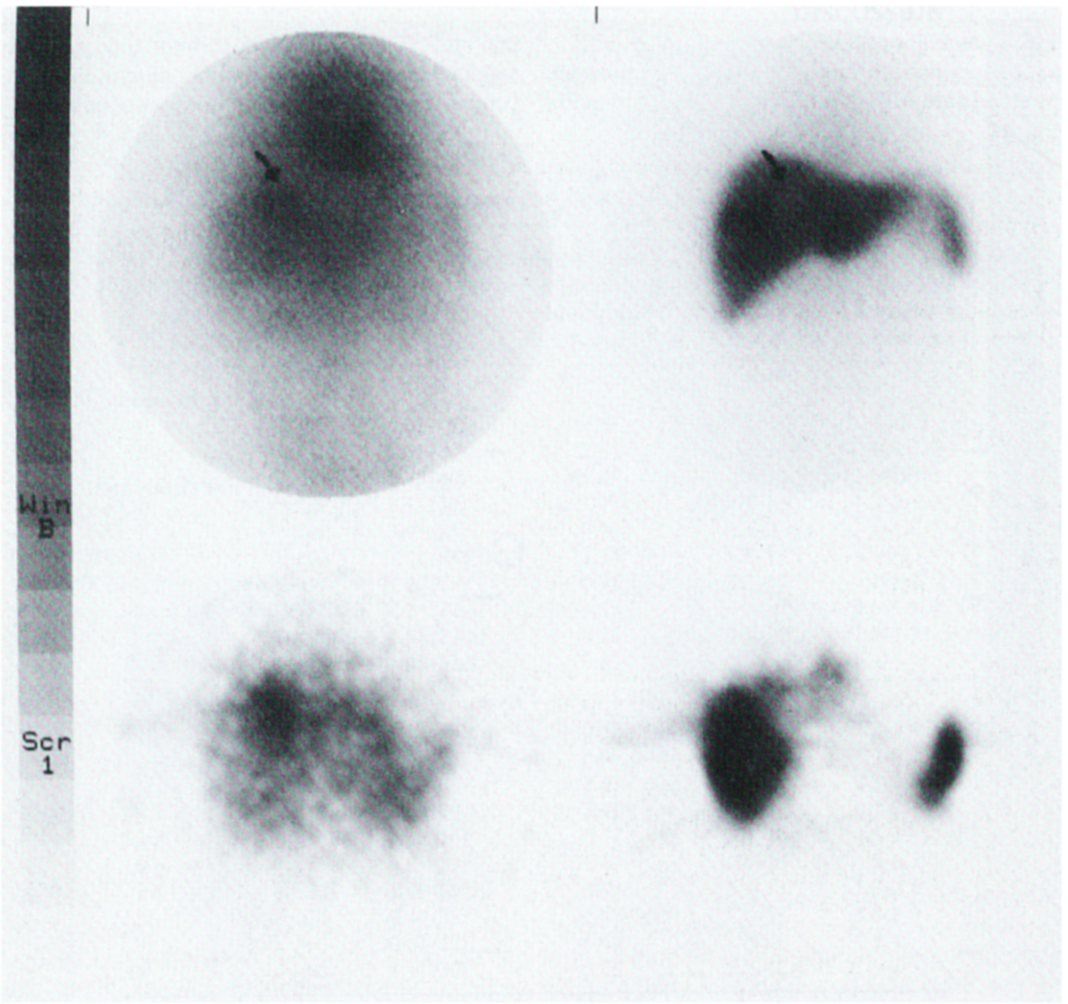

Fig. 3. Images obtained in patient number 2 of the group who received intact Mab. Upper left: planar incidence of ^{131}I-Mab distribution at day 3. The arrow indicates a hepatic metastasis. Lower left: transaxial tomographic slice at the level of the metastasis. Right column: colloid injection, providing anatomical landmarks (normal liver and spleen).

Plasma kinetics and imaging studies

Clearance of ^{131}I-Mab from the blood (Fig. 1) showed a half-life from 1 to 2.3 days for intact antibodies with a mean of 1.6 days, while for $F(ab')_2$ fragments (Fig. 2), this half-life ranged from 0.7 to 1.6 days with a mean of 1.2 days. As expected, there was a trend to a higher circulating half-life for intact Mab but the difference between the two groups was not significant. Scintigraphic studies detected most of the metastases, especially with tomoscintigraphic images, but in 5 cases surgery discovered more metastases than visualised on immunoscintigraphy. An example of images obtained after injection of intact Mab and $F(ab')_2$ fragments is shown, respectively, in Figs 3 and 4. In 1 patient, laparotomy was indicated because of CEA increase with a negative workup (echography, computed tomography, endoscopy); in this case tomoscintigraphy showed a hyperfixation which was confirmed by surgery to be a liver metastasis of 2 cm.

Concentration of ^{131}I-Mab was maximal in vascular compartment 2–4 hours after infusion. Liver metastases were clearly detectable at day 2 and later as progressively increasing hyperfixations when compared to surrounding structures.

Direct measurement of radioactivity in resected tissues

Uptake was expressed in percentage of the injected dose $\times 10^{-3}$ g in different fragments of metastases and from normal liver. The concentration in metastases varied from 0.34 to 4.92 with intact antibodies (Fig. 5) and from 0.33 to 4.64 with $F(ab')_2$ (Fig. 6). This concentration was dependent on the delay between surgery and antibody administration which varied from 3 to 8 days. There was a great variation in distribution of radiolabelled antibodies between metastases in the same patient. The size of metastases was a determinant factor and correlated with a relatively low uptake of antibody concentration. For example, patient no. 1 who received intact Mab had multiple metastases, two of which were analysed: one of 3 cm diameter was biopsied and another (diameter less than 0.5 cm, weighing 0.1 g) was completely resected. Radioactivity was 5.18 kBq (0.14 μCi) per gram for the first and 38.1 kBq (1.03 μCi) for the other with a tumour to liver ratio of 2.8 and 21.6, respectively. In addition, antibody uptake was about two times higher in the periphery than in the core of resected tumour. This difference was well correlated with the percentage of necrotic cells which was found to be higher in the core of the tumour.

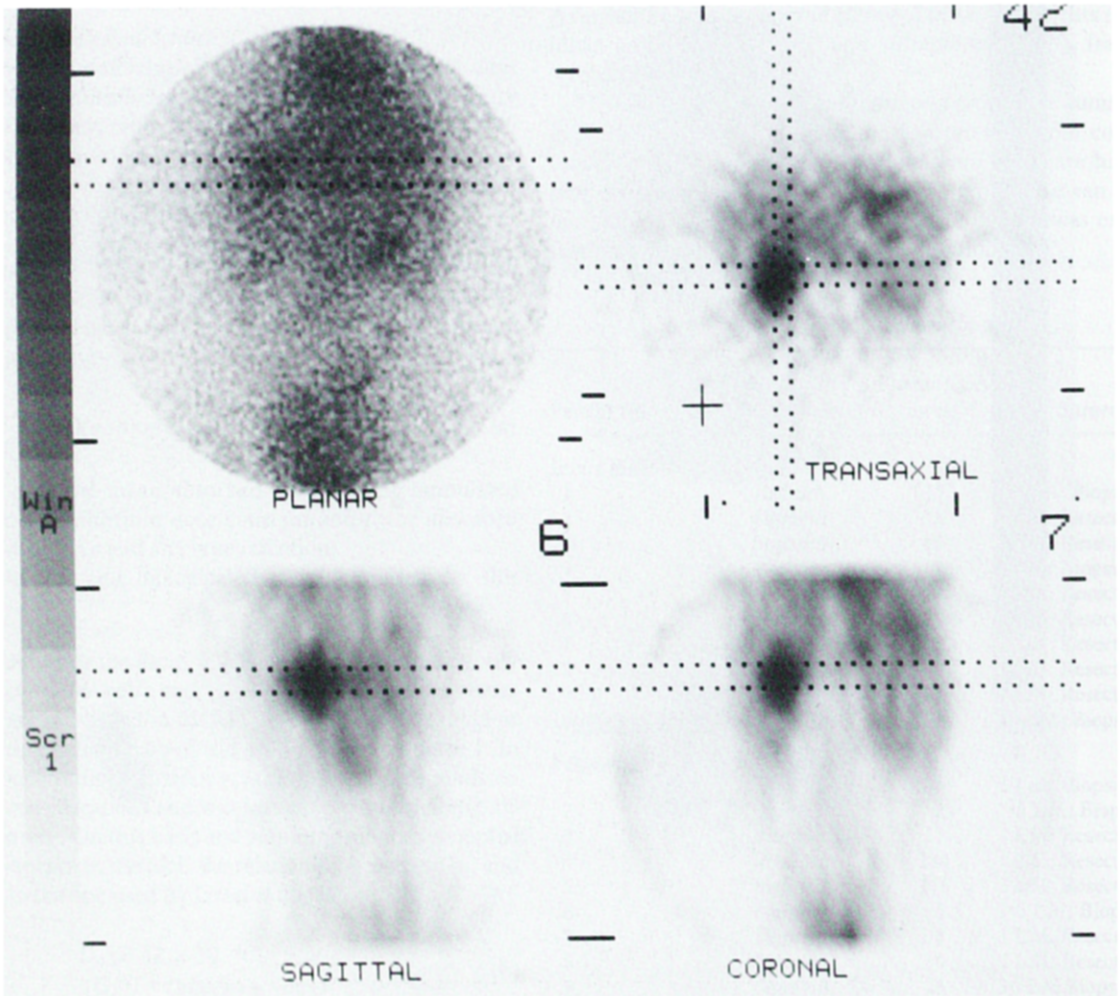

Fig. 4. Images obtained in patient number 3 of the group who received $F(ab')_2$ fragments. Planar image of the ^{131}I-Mab distribution and transaxial, sagittal and coronal tomographic slices at the level of a hepatic metastasis.

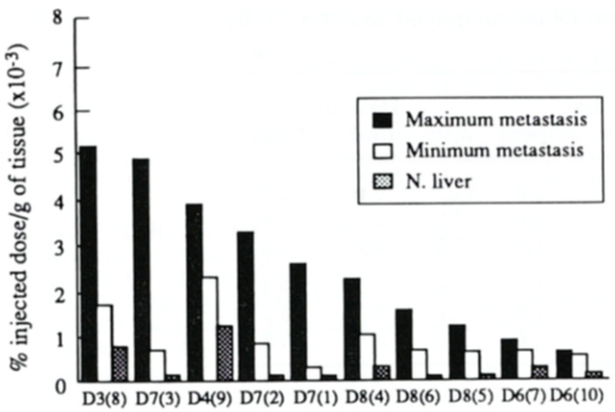

Fig. 5. Distribution of ^{131}I in tissue samples for patients injected with intact Mab. D*n* represents the number of days between injection and surgery, while the number in parenthesis corresponds to the patient number of entry in the study.

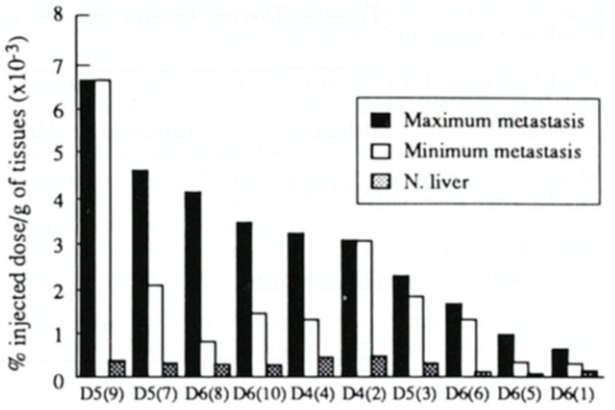

Fig. 6. Distribution of ^{131}I in tissue samples for patients injected with $F(ab')_2$ fragments, as in Fig. 5.

For all metastases, tumour to normal liver ratio was higher than one, ranging from 1.8 to 33. Tumour to fat or tumour to muscle ratios were always 10 times higher than tumour to normal liver ratio.

Dosimetric studies

By taking into account tomoscintigraphic SPECT data and radioactive measurements in tissue samples, we could estimate mean organ dose and tumour dose for patients with a good tracer uptake. Table 3 resumes the effective half-life from tomoscintigraphic data and corresponding dose calculations.

There was no correlation between the effective half-life and radioactive uptake even when the data were corrected for radioactive decay. In addition, due to the dosimetric model used in this study, it is not possible to take into account the heterogeneity of the Mab distribution.

DISCUSSION

The major clinical studies of radioimmunotherapy concern hepatocarcinomas [3, 18] and ovarian carcinoma [19–21]. In colon cancer, radiolabelled anti-CEA Mab have been used for 10

Table 2. Distribution of ^{131}I-Mab in patients

Patient no.	Dose (mg)	Activity* GBq (mCi)	Mean value in % of injected dose $\times 10^{-3}$/g tumour tissue	Tumour to liver ratio†	Tumour to blood ratio‡
Intact Mab					
1	30	1.48 (40)	1.32	2.8–21.6	1.4–10.3
2	30	1.11 (30)	2.31	5.4–20.6	1–3
3	30	1.48 (40)	1.85	4.8–33	1.5–10.4
4	30	1.11 (30)	1.75	3.1–6.8	1.2–2.9
5	30	0.85 (23)	0.91	5–9.3	1–1.3
6	30	1.22 (33)	1.14	5.8–13	—
7	30	1.22 (33)	0.77	2.3–3	1–1.2
8	30	1.2 (32.5)	4.13	2.2–6.4	0.6–1.9
9	30	1.07 (29)	3.28	1.8–3.2	1.1–1.7
10	30	1.05 (28.5)	0.63	3.2–3.8	—
Fragment Mab					
1	30	1.11 (30)	0.47	2–4	1.2–2.4
2	15	0.55 (15)	3.06	6.6	1.6
3	30	1.40 (38)	2.13	5.6–7	2.3–2.8
4	30	1.09 (29.5)	2.41	3–7	1–2.4
5	30	0.96 (26)	0.57	3.8–10	4.5–13.5
6	30	0.85 (23)	1.47	10–13	5–6.5
7	30	1.09 (29.5)	3.49	6.1–13.7	1.2–2.6
8	30	1.40 (38)	2.47	2.6–13	0.8–3.9
9	60	0.81 (22)	6.60	16	2.4
10	60	1.11 (30)	2.63	5.2–12.4	—

*Injected at day 0.

†Lower and higher value of the ratio in the same patient.

Table 3. Effective half-life and dose estimations for an extrapolated dose of 3.7 GBq (100 mCi)

Mab type	Patient no.	T_{eff} (day) Meta	Liver	Spleen	Dose (Gy) Meta	Liver	Spleen
Intact Mab	3	3.2	1.9	2.0	11.5	0.5	0.5
	5	3.3	2.0	2.0	3.5	0.4	0.4
	6	3.2	1.9	1.8	5.5	0.6	0.6
Fragment Mab	3	3.8	1.7	1.7	3.4	0.3	0.3
	7	2.7	1.8	1.8	7.1	0.7	0.7
	8	4.3	2.6	2.6	8.2	0.5	0.5

years for immunoscintigraphy with encouraging results [22–24]. Experimental studies of radioimmunotherapy in nude mice were very promising using ^{131}I-labelled Mab [1, 2]: radiation dose obtained in the tumour was about 83 Gy for an injection of 81.4 MBq (2.2 mCi) of ^{131}I anti-CEA F(ab')$_2$ and only 6.2 Gy to the liver.

Our clinical dosimetric results show lower absorbed doses: in tumours, radiation dose was about 10 Gy per 3.7 GBq (100 mCi) of ^{131}I anti-CEA MAb injected. This was greatly dependent on Mab uptake which was higher for very small metastases and lower for large and necrotic tumour masses, and higher in the periphery of the tumour than in its core, suggesting that micrometastases with actively dividing tumour cells could more intensively concentrate ^{131}I-Mab than macroscopic metastases. These results are in agreement with the recent dosimetric results reported by Siegel *et al.* [25]. On the other hand, our results are encouraging in terms of tumour to normal liver ratio of radiolabelled antibody and demonstrate that it is possible to inject a great quantity of ^{131}I anti-CEA Mab without hepatic toxicity. Another encouraging point was the low radiation dose calculated for the spleen which may be considered to be similar for bone marrow absorbed radiation dose [26]. However, considering radiosensitivity of bone marrow, no more than 11.1 GBq (300 mCi) could be injected without great risk of aplasia. Thus, 11.1 GBq of ^{131}I-labelled anti-CEA Mab or fragments should be the maximally tolerated dose. According to values extrapolated from the results of our trial no more than 30 Gy would be delivered to the tumour with this amount of radiolabelled antibody. We should, therefore, conclude that a dose tolerable to the bone marrow would probably not be sufficient to effect macroscopic metastases. Interestingly, in a recent clinical study of patients with non-Hodgkin lymphoma, Press *et al.* [5] used escalating doses (275–910 mg) of anti-CD37 Mab labelled with 9.25–22.5 GBq (250–608 mCi) of ^{131}I. They obtained complete remissions in 4 of the 5 patients treated. Myelosuppression was the only significant acute toxicity but all patients underwent autologous bone marrow harvest before treatment and two required reinfusion of bone marrow. Such an approach could be used for radioimmunotherapy of colorectal carcinoma although this seems to be far less radiosensitive than lymphoma.

Finally, we may draw four conclusions from this study:

—It is possible, in clinical conditions, to concentrate ^{131}I anti-CEA antibodies B7-35 and F6 selectively in liver metastases from colorectal carcinoma with a tumour to normal liver ratio greater than 5 in the majority of cases. This corresponds to the lower limit recently proposed by Welt *et al.* [27] for the screening of antibodies in radioimmunotherapy.

—There is great heterogeneity of radioactivity distribution in metastases.

—Bone marrow would be the only likely site of acute radiotoxicity in patients injected for therapy with high activities of ^{131}I anti-CEA Mab.

—Radiation dose delivered to the tumour tissue is not sufficient to effect macroscopic non-resectable metastases from colon carcinoma, but the dose may have a potential effect upon microscopic metastases. This form of radioimmunotherapy may offer an advantage when combined with other treatment modalities.

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Acknowledgements—This study was partly supported by the Association pour la Recherche sur le Cancer.

Eur J Cancer, Vol. 29A, No. 8, pp. 1111–1114, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Clinical Heterogeneity of Hereditary Breast Cancer and its Impact on Screening Protocols: The Dutch Experience on 24 Families under Surveillance

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We investigated 24 families who satisfied a set of criteria for hereditary breast cancer. Five families had only breast cancer, four a combination of breast and ovarian cancer and the remaining 15 had also a variety of other cancers. The families include 86 patients, 78 of which had a malignant tumour and the rest had a benign lesion in the breast. The median age at diagnosis of the breast cancer was 47 years. Three of the 24 families were of a late onset variant. 58 of the 86 patients were symptomatic while 18 were identified during presymptomatic screening because of a positive family history. In 10 cases the reason for referral was not known. 56 of the symptomatic patients had a malignant breast lesion, 52% of which were with lymph node metastasis whereas 12 of the screening group had breast cancer with 2 patients showing lymph node involvement ($P = 0.06$). 22 of the symptomatic patients and none of the screening patients died of breast cancer after a median observation period of 6 and 7 years, respectively ($P < 0.05$).
Eur J Cancer, Vol. 29A, No. 8, pp. 1111–1114, 1993.

INTRODUCTION

OF ALL the breast cancer cases, 5% are due to hereditary causes [1, 2]. Hereditary breast cancer (HBC) is characterised by an early age of onset and a high incidence of bilateral tumours [3, 4]. Based on the association of breast cancer with other cancers HBC can operationally be subclassified into various categories. For example, the combination of breast cancer with sarcoma, brain tumour, lung cancer, adrenocortical carcinoma and leukaemia is designated as the Li–Fraumeni syndrome [5]. Another association of breast cancer is with ovarian cancer [6]. Surveillance in HBC may lead to the early detection of tumours and thus might improve the prognosis. An understanding of HBC heterogeneity with respect to its association with various other cancers and the variation in the age of onset is of paramount importance in developing appropriate management and surveillance protocols. Therefore, we set up a collaborative study in 24 suitable families to analyse the association of HBC with other cancers, to assess the age of onset of breast cancer and to evaluate