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Prednimustine (Sterecyt) Versus Cyclophosphamide Both in Combination with Methotrexate and 5-Fluorouracil in the Treatment of Advanced Breast Cancer

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153 women with advanced breast cancer were randomly allocated for treatment with SMF [prednimustine (Sterecyt) + methotrexate + 5-fluorouracil, 83 patients] or CMF (cyclophosphamide + methotrexate + 5-fluorouracil, 70 patients). Prednimustine was administered orally 100 mg/m² daily, for 5 days, and cyclophosphamide was administered orally 100 mg/m², for 14 days, each, every 4 weeks. Methotrexate was given at a dose of 40 mg/m² and 5-fluorouracil at 600 mg/m² on day 1 and 8, every 4 weeks. Leucovorin was used in 39 patients to alleviate mucositis. The two treatment groups were balanced in terms of age, performance status, lymph node status, histology, menopausal status and previous therapy. Response was evaluated in 140 patients. Of 76 patients treated with SMF, 4 had a complete and 21 a partial response (CR + PR = 33%), 40 had no change (NC) and 11 had progressive disease (PD). Of 64 patients treated with CMF, 3 had a complete and 18 a partial response (CR + PR = 33%), 30 had no change (NC) and 13 had progressive disease (PD). Time to treatment failure and survival were similar in both groups. A relationship between haematological and gastrointestinal toxicity and therapeutic efficacy was demonstrated with a superior survival and response rate recorded for patients with such toxicity than in patients without. Haematological toxicity was, in general, mild to moderate with no difference between the two groups. Alopecia ($P = 0.008$), nausea/vomiting ($P = 0.02$) and euphoria ($P = 0.03$) were more common in the CMF-treated group. Diarrhoea was more common in the SMF group ($P = 0.03$). In conclusion, SMF seems to be as efficient as CMF with regard to response rate, time to treatment failure and survival. However, SMF was tolerated better than CMF.
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INTRODUCTION

IN SPITE of the many studies carried out in patients with advanced breast cancer, there is as yet no general agreement on how such patients should be treated. Treatment results on the whole leave much room for improvement regarding efficacy as well as tolerance to the chemotherapeutic regimen.

Prednimustine (Sterecyt), an ester of chlorambucil and prednisolone, has been shown to be effective as a single agent in advanced breast cancer with response rates ranging from 9 to 49% [1–3]. In a comparative study, prednimustine was more effective than its constituents chlorambucil and prednisolone [4]. Cyclophosphamide has been extensively studied in advanced breast cancer and its activity as a single agent is reported to be 34% [5, 6].

CMF (cyclophosphamide, methotrexate and 5-fluorouracil) is one of the most widely used chemotherapeutic combinations in the treatment of breast cancer, and it has been extensively studied [7]. Cyclophosphamide is considered to give a substantial contribution to the efficacy of CMF, although methotrexate and 5-fluorouracil also possess single agent activity [8, 9]. However, side-effects, such as alopecia, nausea and vomiting, are drawbacks with this combination. A preliminary clinical trial was designed in order to find a new multidrug regimen that would be better tolerated. Prednimustine, methotrexate and 5-fluorouracil (SMF) were thus combined and the results indicated that this combination was effective and well tolerated [10].

The present study of SMF versus CMF was then designed in order to compare the efficacy and the toxicity between the two multidrug regimens. The dose limiting toxicity of both cyclophosphamide and prednimustine is bone marrow suppression, and the doses selected for this trial were based on experience of haematological toxicity.

PATIENTS AND METHODS

153 patients were recruited between February 1983 and June 1987. Eligible patients had histologically verified breast cancer with objective evidence of new lesions appearing or existing

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lesions enlarging and with spread beyond the original site of tumour, and no prior treatment with cytotoxic drugs (with the exception of adjuvant chemotherapy).

Patients were randomly allocated to SMF or CMF and stratification was performed according to menopausal status, dominant site of disease and participating centre. Prednimustine was given in oral doses of 100 mg/m^2 on days 1–5 and cyclophosphamide in oral doses of 100 mg/m^2 on days 1–14. Methotrexate was given in intravenous (i.v.) doses of 40 mg/m^2 on days 1 and 8 and 5-fluorouracil (5-FU) in i.v. doses of 600 mg/m^2 on days 1 and 8. The courses were repeated every 4 weeks. In case of leukopenia and/or thrombocytopenia, the dosage was reduced for all three drugs in the combinations. If the white blood cell count (WBC) was 3.0 × 10^9/l or more and platelets were 100 × 10^9/l or more, the full dose was administered. If WBC was 2.0–2.9 × 10^9/l and/or platelets were 50–99 × 10^9/l, 50% of the full dose was given. If lower WBC and/or platelets were encountered, treatment was delayed and blood counts performed once a week. In one institution (Belvidere), where 18 patients were randomised to CMF and 21 to SMF, leucovorin 15 mg was given 6-hourly for six doses starting 24 h after administration of methotrexate to all included patients in order to minimise mucositis. Blood counts were made on days 1, 8 and 28. Assessment of response was made according to WHO and UICC criteria [11, 12]. Oral informed consent was obtained from all patients.

Statistical evaluation of patient characteristics, response categories and side-effects was made by use of the Mann–Whitney U-test and χ^2 test, whereas the Breslow test was used for analysis of time to treatment failure and survival.

RESULTS

Patients' characteristics are summarised in Table 1. 83 patients were randomised to treatment with SMF and 70 to CMF.

Table 1. Patients' characteristics

	SMF	CMF	Total	Mann–Whitney U-test
No. entered	83	70	153	
Age at entry (median years)	60	58	59	N.S.
Performance status (ECOG)				
0	20	22	42	
1	41	32	73	N.S.
2	15	11	26	
3	7	5	12	
Premenopausal	15	10	25	
Perimenopausal	17	16	33	N.S.
Postmenopausal	51	44	95	
				χ^2
Soft tissue involvement	63	56	119	
Dominant	19	20	39	N.S.
Bone involvement	40	28	68	
Dominant	20	15	35	N.S.
Visceral involvement	50	41	91	
Dominant	44	35	79	N.S.
Liver	10	6	16	
Lung	33	23	56	
Liver and lung	1	6	7	
Pleura	4	5	9	
Other	2	1	3	

N.S. = not significant.

The difference in patient number between the groups is due to the cumulation of small differences at a majority of the institutions. Violations of the randomisation procedure have not been detected. The median age at diagnosis was 55 years (range 24–75) and at entry into the study 59 years (range 25–79). Median performance status was 1 (range 0–3). Age and performance status were equal in the two groups.

25 patients were premenopausal, 33 peri- and 95 post-menopausal at entry into the study. There was no difference between the groups in this regard. Histological sub-types were well balanced between both treatment groups.

Lymph node involvement at entry was present in 38 SMF and 42 CMF treated patients, absent in 27 SMF versus 14 CMF treated patients and unknown for 18 SMF and 14 CMF patients. Thus, fewer patients in the SMF arm had lymph node involvement, although soft tissue involvement as a whole was well-balanced between the two groups.

39 patients had soft tissue as the dominant site of disease, whereas 35 had bone and 79 had viscera as the dominant disease site. The treatment groups were equal regarding the dominant site of disease. 40 SMF versus 28 CMF treated patients had bone metastases, a difference that was not statistically significant. 119 patients had soft tissue and 79 patients had visceral involvement with no difference between the treatment groups.

Table 2 shows that 66 SMF and 58 CMF patients had had surgery, 41 SMF and 47 CMF patients had had radiotherapy and 69 SMF and 60 CMF patients had received endocrine therapy. Median time from start of primary therapy to first recurrence was 1.8 years (range 0–18) with no difference between the groups.

3 patients in the SMF group were ineligible. 1 received other chemotherapy concomitantly and 2 had brain metastases at entry to study. 10 patients were not evaluable for response, 4 SMF and 6 CMF: 1 patient died of primary disease before receiving any chemotherapy (CMF), 5 patients were withdrawn within 5–39 days due to cardiovascular disease (2 CMF, 3 SMF), 2 patients were withdrawn on days 28 and 42 due to severe depression (2 CMF), 1 patient had concomitant therapy with tamoxifen (SMF) and 1 patient had her only measurable lesion in soft tissue removed by biopsy (CMF).

Overall response is shown in Table 3. Of the 140 patients evaluable for response, 76 received SMF and 64 received CMF. In the SMF group, 4 patients (5%) showed complete response and 21 (28%) partial response with an overall response rate of 33%. There was stable disease in 40 (53%) while disease progressed during treatment in 11 patients (14%). 4 patients were not evaluable, and 3 were not eligible in the SMF randomisation group.

In the CMF group 3 patients (5%) had a complete response and 18 (28%) a partial response with an overall response rate of 33%. 30 patients (47%) had stable disease and 13 patients (20%)

Table 2. Primary therapy

	SMF	CMF	Total	Mann–Whitney U-test
Surgery	66	58	124	N.S.
Radiotherapy	41	47	88	$P = 0.06$
Endocrine therapy	69	60	129	N.S.
Adjuvant chemotherapy	0	2	2	

Table 3. Overall response

	SMF	CMF	Total	Mann–Whitney U-test
Complete response	4	3	7	
Partial response	21	18	39	
No change	40	30	70	N.S.
Progressive disease	11	13	24	
Not evaluable	4	6	10	
Not eligible	3	0	3	
Total	83	70	153	

Table 4. Response in soft tissue

	CMF	SMF	Total	Mann–Whitney U-test
Complete response	12	8	20	
Partial response	13	18	31	
Progressive disease	4	5	9	N.S.
Not evaluable	5	5	10	
Total	56	63	119	

had progressive disease during treatment. 6 CMF patients were not evaluable for response. The results were thus similar in the two groups.

Assessment of response according to the dominant site of disease showed no significant difference between the two groups. Response rate (CR + PR) was 43% in soft tissue, 10% in bone (radiographic assessment) and 18% in visceral disease (Tables 4–6).

Median overall survival (OS) was 338 (SMF) vs 324 days (CMF), respectively (Fig. 1). The medium time to treatment failure (TTF) was 130 days for SMF and 132 days for CMF

Table 5. Response in bone

	CMF	SMF	Total	Mann–Whitney U-Test
Complete response	3	4	7	
No change	12	20	32	
Progressive disease	4	5	9	N.S.
Not evaluble	9	11	20	
Total	28	40	68	

Table 6. Response in viscera

	CMF	SMF	Total	Mann–Whitney U-test
Complete response	1	2	3	
Partial response	5	6	11	
No change	14	21	35	N.S.
Progressive disease	9	5	14	
Not evaluable	6	10	16	
Total	35	44	79	

Table 7. Maximum level of toxicity over all courses of therapy

	SMF	CMF	Total	Mann–Whitney U-test
No. of treated patients	83	69	152	
Haemoglobin > 11.0g/dl	28	25	53	N.S.
9.5–10.0 g/dl	24	12	36	
< 9.5 g/dl	5	1	6	
WBC nadir 10^9/l, > 4.0	30	22	52	
3.0–3.9	24	22	46	
2.0–2.9	20	16	36	N.S.
1.0–1.9	1	1	2	
< 1	1	0	1	
Platelet nadir 10^9 cells/l, > 100	79	58	145	
75–99	2	0	2	
50–74	1	1	2	N.S.
25–49	0	0	0	
< 25	1	2	3	
Alopecia				
None	26	15	41	
Minimal	27	16	43	
Moderate, patchy	27	25	52	$P = 0.008$
Complete, reversible	3	12	15	
Complete, irreversible	0	1	1	
Nausea/vomiting				
None	17	10	27	
Nausea	27	12	39	
Transient vomiting	25	29	54	$P = 0.02$
Requiring therapy	9	12	21	
Intractable	5	6	11	
Diarrhoea				
None	61	60	121	
< 2 days	6	6	13	
Tolerable > 2 days	10	0	10	$P = 0.03$
Intolerable, requiring therapy	5	3	7	
Haemorrhagic, dehydration	1	0	1	
Stomatitis				
None	71	56	127	
Soreness/erythema	2	2	4	
Ulcers, can eat solids	4	4	8	N.S.
Ulcers, liquid diet	6	6	12	
Parenteral nutrition	0	1	1	
Euphoria				
0 none	76	55	131	$P = 0.03$
1 tendency	7	12	19	
2 marked	0	2	2	
Anxiety				
0 none	41	38	79	
1 tendency	22	12	34	
2 marked	16	14	30	N.S.
3 distressing	4	4	8	
4 disabling	0	1	1	
Depression				
0 none	45	32	77	
1 tendency	16	19	35	
2 marked	19	11	30	N.S.
3 distressing	3	6	9	
4 disabling	0	1	1	

treated patients. TTF and OS were analysed according to intention to treat, i.e. $n = 153$.

Dose limiting toxicity may be used as an indicator of treatment intensity. Obviously, there is a relationship between the dose and the haematological toxicity of SMF and CMF. However, a number of patients withdrew from the study due to gastrointesti-

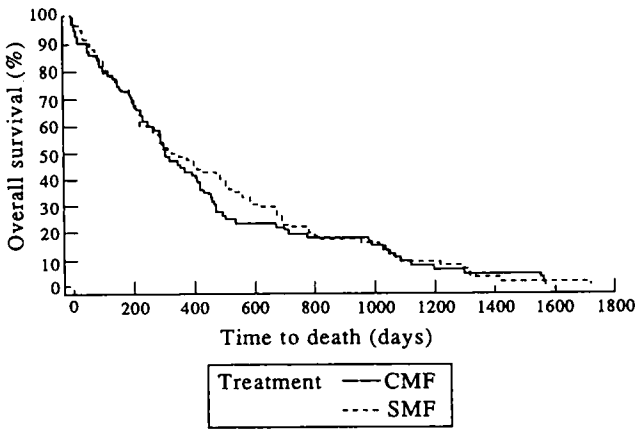

Fig. 1. Overall survival for 83 SMF and 70 CMF treated patients, analysed according to intention to treat, i.e. all randomised patients.

nal (GI) toxicity, which also may be regarded as dose-limiting. Of GI toxicities only nausea/vomiting was frequent enough to make a statistically meaningful comparison possible. Likewise, only leukopenia could be analysed since thrombocytopenia was too rare.

137 patients had one or more recordings of WBC after start of treatment. 98 patients had recordings of WBC according to WHO grade 0 or 1, i.e. no or only mild leukopenia was noted during the treatment. Such patients had a median time to treatment failure of 128 days. The remaining 39 patients had recordings of worst toxicity as WHO grade 2 or more, i.e. moderate or severe leukopenia was registered, and had a median time to treatment failure of 201 days, $P = 0.003$. Median overall survial for patients with leukopenia grade 0 to 1 was 336 days as compared with 454 days for patients with grade 2–4, $P = 0.05$.

The response rate for patients with any recording of leukopenia grade 1 or more was 39% as compared with 29% for patients without leucopenia, $P = 0.03$ (Fig. 2).

152 patients had presence or absence of nausea/vomiting recorded after start of treatment (Table 7). For 66 patients with nausea grade 0 or 1, median time to treatment failure was 110 days, whereas 86 patients experiencing grade 2–4 nausea/vomiting had a median time to treatment failure of 148 days, $P = 0.0025$. Median overall survival for patients with nausea grade 0–1 was 268 days as compared with 423 days for patients with grade 2–4 nausea/vomiting, $P = 0.002$.

Response rates for patients with grade 0–1 vs. grade 2–4 nausea/vomiting were equal, 33% in each group.

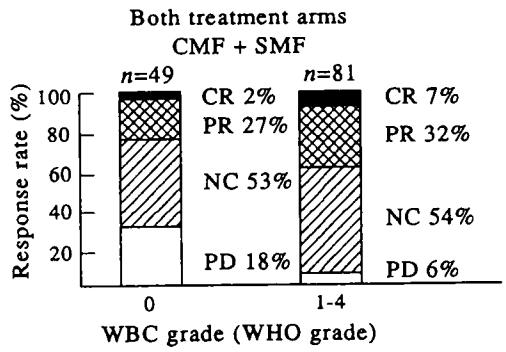

Fig. 2. Response rate vs. highest WHO grade of nadir WBC during therapy.

Toxicity

The maximum level of toxicity for all courses of therapy is summarised in Table 7. A total of 856 SMF courses were given as compared with 710 CMF courses. A median of 8 (mean = 10) courses were given per patient in each treatment arm. 147 (17%) SMF and 178 (25%) CMF courses were given at a reduced dosage. 10 CMF and 5 SMF patients withdrew from the study because of toxicity which was mainly gastrointestinal. Haematological toxicity was in general mild to moderate. Haemoglobin values were retrievable in 152 patients. Only 6 patients had any recording below 9.5 g/dl. WBC counts were recorded for 137 patients. 3 patients had WHO grade 3 or 4 leukopenia. 152 patients had recordings of platelet counts, 3 of whom had WHO grade 4 toxicity. Thus, only 2% of patients had severe or very severe bone marrow depression. There were no significant differences between the two groups regarding haematological toxicity.

Alopecia was clearly more severe in the CMF than in the SMF group, $P = 0.008$, and nausea/vomiting was also more pronounced among CMF than SMF treated patients, $P = 0.02$. Diarrhoea, grade 2–4, was more prevalent among SMF than among CMF treated patients, $P = 0.03$. This was predominantly in the centre using Calcium Leucovorin (10/21 SMF patients and 3/18 patients in the CMF group). Stomatitis was equally common among CMF and SMF treated patients as was also depression and anxiety, whereas euphoria was more common in the CMF than in the SMF group, $P = 0.03$. Other toxicity was in general mild and infrequent.

Thus, non-haematological toxicity was more frequent in CMF than in SMF treated patients.

DISCUSSION

This study showed that prednimustine in this dosage was as effective as cyclophosphamide in standard doses but less toxic when used in combination with methotrexate and 5-FU for treatment of patients with advanced breast cancer. The response rate was identical in the two treatment groups but lower than otherwise reported for both CMF and SMF. Ordinarily CMF is reported to give approximately 50% objective remissions (CR + PR) in the treatment of advanced breast cancer [7, 13–15] although a response rate similar to that in this study has been reported [16]. The response rate of CMF is similar to that reported for other commonly used combinations, such as 3M, (mitozentrone, methotrexate, mitomycin C) and VAC (vincristine, doxorubicin, cyclophosphamide) [17, 18] but slightly inferior to that reported for CAF (cyclophosphamide, doxorubicin, 5-FU) [19, 20]. In one previous study of SMF a response rate of 75% was found [10]. These differences may be partly due to differences in the patient populations. The majority of the patients in the present study had received prior endocrine therapy and a large number had also received prior radiotherapy.

Haematological and gastrointestinal toxicity were used as indicators of treatment intensity, since they constitute biological parameters of the amount of cytotoxic therapy that has actually reached sensitive cells in the body. The number of dose reductions only reflects the accuracy of the initial dose recommendations according to the trial protocol influenced by institutional therapeutic policies. Therefore, the number of dose reductions may have limitations as a parameter for comparison of treatment intensity between two different regimens.

Response rate, OS and TTF were superior for patients who had experienced leukopenia than for those who had not, which is a validation of haematological toxicity as an index for monitoring

treatment intensity with chemotherapeutics. There was no difference in the incidence of leukopenia between the two groups, which indicates that treatment intensity was equal. Haematological toxicity was low in this study which may partly explain the relatively low response rate.

Nausea and vomiting was also related to a superior overall survival and time to treatment failure, even though response rates were equal for patients with or without vomiting. Nausea/vomiting as well as haematological toxicity seems to be useful indicators of treatment intensity for drugs that are associated with this side-effect as a function of dose. The results of the present study suggest that cyclophosphamide is more prone to give rise to nausea and vomiting than prednimustine at doses that are equitoxic regarding bone marrow suppression.

The relationship between dose intensity and therapeutic efficacy has been subject to a number of recent studies [21–23] and forms part of the rationale for the use of very high dose chemotherapy followed by haematopoietic growth factor [24] or autologous bone marrow support [25].

Cyclophosphamide has probably the highest single agent activity of the drugs in the CMF combination [5] and, therefore, stands for a significant contribution to the overall antitumour efficacy of CMF. With prednimustine being as effective as cyclophosphamide in this study, it seems reasonable to conclude that prednimustine also stands for a significant contribution to the antitumour efficacy of SMF. It may be argued that chlorambucil plus prednisolone should have been used instead of prednimustine in this comparison with cyclophosphamide. However, in a previous study, prednimustine showed superior efficacy as compared with the combination of chlorambucil and prednisolone [4]. Therefore, prednimustine was considered as an appropriate agent for this comparison.

Non-haematological toxicity of SMF was less than that of CMF. In the SMF group significantly less alopecia and nausea/vomiting was reported than for patients on CMF. In a previous study even less nausea/vomiting was reported after SMF treatment [10]. In the present study diarrhoea was more common in the SMF than in the CMF group which is not in accordance with the results of a previous study [10], where this side-effect was not seen. The higher incidence of diarrhoea in the study is likely to be due to the use in one centre of calcium leucovorin following methotrexate which is now known to enhance the action and toxicity of 5-FU [26]. Other toxicities were, in general, mild and infrequent. Chlorambucil has been used in combination with methotrexate and 5-FU in adjuvant chemotherapy of breast cancer [27]. This regimen was not so well tolerated because of a high incidence of nausea and vomiting. However, efficacy and toxicity can only be compared within a prospective randomised trial, and therefore, conclusions cannot be drawn from this discrepancy. On the whole, this study confirms earlier findings of SMF as a reasonably well tolerated regimen for advanced breast cancer.

In conclusion, prednimustine used in combination with methotrexate and 5-FU (SMF) was as effective as cyclophosphamide used with the same combination (CMF) in terms of response rate, time to progression and survival. SMF was less toxic than CMF with respect to non-haematological toxicity such as alopecia, nausea and vomiting. The combination of prednimustine, methotrexate and 5-FU, therefore, seems to be appropriate for routine treatment as well as for further clinical studies on patients with advanced breast cancer.

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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

Marc Ychou, Marcel Ricard, Jean Lumbroso, Philippe Rougier, Jean-Pierre Mach, Franz Buchegger, Jean-Claude Saccavini, Philippe Lasser, Dominique Elias, François Eschwege and Claude Parmentier

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.
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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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