International Symposium on Labeled and Unlabeled Antibody in Cancer Diagnosis and Therapy

1990年2月9日





International Symposium on Labeled and Unlabeled Antibody in

Cancer Diagnosis and Therapy



in Memory of

Mr. Gordon Dalsemer and Mr. Dale Tooley who contributed to society in many ways and shared with their families the desire for new cancer therapy

Turner Auditorium
The Johns Hopkins Medical Institutions
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INTRODUCTION

The International Symposium on Labeled and Unlabeled Antibody in Cancer Diagnosis and Therapy represents the first meeting of investigators in the major disciplines to analyze the potential use of antibody for diagnostic and therapeutic applications in cancer therapy. In the development of antibody technologies and applications, the degree of quantitative analysis has not been sufficient to further advance this new clinical science, and it has not been commensurate with the significant amount of clinical experience. The general lack of acute symptoms associated with the use of labeled and unlabeled antibodies, the relative safety of the therapy, and the discrete specificity of antibodies for antigens existing in a variety of malignant disorders proffer wide potential for both basic and applied scientific endeavor.

As a step toward integrating disciplines such as immunology, radiobiology, and physics with the clinical evaluations and analyses offered by nuclear medicine, medical oncology, and radiation oncology, the proceedings from this symposium summarize the experience in these fields and bring together the broadest scope of information available for both clinical scientists and laboratory researchers. This monograph contains reports on 1) applications of unlabeled antibody in bone marrow transplantation; 2) isotopic applications in nuclear scanning for diagnosis, the delivery of chemotherapeutic drugs with antibody, and the use of radiolabeled antibody in therapeutic applications; 3) new radiobiologic information regarding low dose rate and the effects of continuous irradiation; and 4) data regarding the developing technologies for quantitation of these various approaches.

It is symbolic of a "new era" in clinical research that this symposium has achieved support from the National Cancer Institute, commercial interests, private contributors, and the academic community. Given time, this clinical science should have a major impact in oncologic practice. The question seems no longer to be "Can we do it?" but rather "How can we do it best?"

We take this opportunity to express our sincere appreciation to all of the sponsors and to all of the investigators who summarized their progress and made this first conference possible.

Stanley E. Order, M.D.

Willard and Lillian Hackerman Professor of Radiation Oncology Department of Radiation Oncology Oncology Center The Johns Hopkins Hospital 600 N. Wolfe St. Baltimore, MD 21205

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Radioimmunoimaging in Malignant Melanoma Patients With the Use of Indium-111-labeled Antimelanoma Monoclonal Antibody (ZME-018) to High-molecular-weight Antigen

James L. Murray, ^{1,*} Michael G. Rosenblum, ¹ Lamk Lamki, ¹ Thomas P. Haynie, ¹ Howard J. Glenn, ¹ Carl E. Plager, ¹ Michael W. Unger, ² Dennis J. Carlo, ² and Evan M. Hersh ¹

ABSTRACT-Radioimmunolocalization of an 111 In-labeled, mouse antimelanoma monoclonal antibody (MAb), ZME-018, was examined in 30 patients with metastatic malignant melanoma. Each patient received a single iv infusion of MAb at concentrations ranging from 0.6 to 40 mg, coupled to 5 mCi 111 In by the chelating agent pentetic acid. No toxicity was observed in an patient. Total-body and region of interest scans performed at 4, 24, and 72 hours following MAb administration revealed uptake in 110 of 171 previously diagnosed metastases for a sensitivity of 64%. Nonspecific uptake of radioactivity was consistently observed in the liver and spleen, and less frequently in the bowel, testes, axillae, and bone. Sensitivity of detection increased significantly at doses of MAb above 2.5 mg, with 74% of the lesions imaging at 20 mg/5 mCi compared with 29% at 2.5 mg/5 mCi (P<.005). Sensitivity actually decreased slightly at the 40-mg dose. There was a significant correlation between tumor uptake of MAb-111 In-conjugate and increasing tumor size. Soft tissue lesions, such as skin and lymph node metastases, were imaged to a greater extent (77%) than were visceral metastases (40%). Mean plasma clearance of ZME-018 was prolonged with a half-life of 33.6 hours in patients receiving 40 mg, compared with 17.8 hours in patients given 2.5 mg (P<.01). Urinary excretion of the isotope averaged 11.4% of the injected dose over 48 hours. Hence radioimmunolocalization of melanoma with ¹¹¹In-ZME-018 appeared feasible. The sensitivity of the technique varies with MAb dose, specific activity of IIIIn-MAb conjugate, tumor size, and disease site.—NCI Monogr 3:3-9, 1987.

The production of murine MAb reactive with a variety of tumor-associated antigens and the development of effective methods for coupling radioisotopes to these MAb without loss of antibody specificity or affinity has generated considerable interest in the use of MAb-isotope conjugates for tumor imaging and therapy in man (I). Investigators conducting recent radioimmunolocalization trials

tigators conducting recent radiominiumolocalization trials

ABBREVIATIONS: MAb=monoclonal antibody; DTPA=pentetic acid; V_d =volume of distribution; $C \times t$ =concentration curve.

1 Departments of Clinical Immunology and Biological Therapy (J. L. Murray, M. G. Rosenblum, and E. M. Hersh); Medical Oncology (C. E.

Plager); and Nuclear Medicine (L. Lamki, T. P. Haynie, and H. J.

Glenn); The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston.

in cancer patients have examined the sensitivity and specificity of tumor localization using either whole MAb or MAb fragments coupled to ¹³¹I (2-4), ¹²³I (5), or ¹¹¹In (6-8).

with other regionaches trans or chraseand examinations.

In this report, we examine the efficacy of imaging metastases in patients with malignant melanoma using an ¹¹¹In-labeled mouse MAb, ZME-018, produced by Hybritech, Inc. (San Diego, CA). An antibody of the IgG2a subclass, ZME-018 is reactive with epitope a of a 240,000-molecular weight antigen (gp240) found on the surface of over 80% of melanoma cell lines and fresh tumor samples (9). Our objectives in this trial were to 1) determine the sensitivity of tumor detection using escalating doses of ¹¹¹In-ZME-018 compared with conventional techniques; 2) determine the toxicity, if any, of the MAb-¹¹¹Iń-conjugate; and 3) measure the overall biodistribution and pharmacokinetics of the ZME-018.

MATERIALS AND METHODS

Preparation of indium-111-labeled ZME-018.—We made the MAb by using conventional hybridoma techniques as described by Wilson et al. (9). Hybridomas were grown as ascites in BALB/c mice, and the antibody was purified from ascitic fluid by sodium sulfate fractionation and DEAE chromatography.

The ZME-018 was conjugated with the chelating agent DTPA by a modification of a technique described by Krejcarek and Tucker (10). Prior to use, 1 mg DTPA-coupled MAb was mixed with 5 mCi⁻¹¹¹In in citrate buffer and, after ¹¹¹In incorporation, the reaction was terminated by an appropriate neutralizing buffer. We then added more unmodified ZME-018 to achieve the desired total antibody dose. The unmodified MAb, the MAb covalently coupled to DTPA, and the ¹¹¹In reagents to be added at the time of study were supplied by Hybritech, Inc.

Patients.—Thirty patients with biopsy-proven, metastatic malignant melanoma received ¹¹¹In-ZME-018 following their written informed consent to a protocol approved in accordance with guidelines established by the Human Investigation Committee at M. D. Anderson Hospital and Tumor Institute. Prior to MAb administration, all patients had a history and physical examination, chest x-ray, electrocardiogram, CBC, platelet count, serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, blood urea nitrogen, creatinine, and urinalysis performed.

Computerized axial tomographic scans of the brain, abdomen, pelvis, and lung (if indicated) were performed

Hybritech, Inc., San Diego, CA.
 * Reprint requests to: James L. Murray, M.D., Department of Clinical Immunology, Box 41, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Ave., Houston, TX 77030.

with other radionuclide scans or ultrasound examinations necessary to document metastatic disease completely.

Study plan.—Patients eligible for study received a single 2-hour infusion of MAb at concentrations of either 0.6 (1 patient), 2.5 (4 patients), 5 (5 patients), 10 (5 patients), 20 (6 patients), or 40 mg (9 patients). The average radioactivity (5 mCi) was constant for each dose. Vital signs were obtained during infusion and following MAb administration. We repeated the CBC, platelet count, serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, blood urea nitrogen, creatinine, and urinalysis at 1, 24, and 72 hours after infusion to monitor toxicity.

Total body imaging was performed with a longitudinal tomographic scanner 2 Phocon 192 from Seiman Nuclear Imaging (Des Plaines, IL).

Region of interest scans were always performed with the use of a General Electric model 400 gamma camera (Milwaukee, WI) and computer-assisted storage from Digital-Gamma 11 (Maynard, MA). Background subtraction techniques were not used. Scans were interpreted by a single nuclear medicine physician who had no previous knowledge of disease sites.

Radiologic methods for indium-111 measurement.— Measurement of ¹¹¹In in serum has been described (11). Heparinized patient blood samples were collected during III In infusion, at the end of infusion (0), and at 1, 5, 10, 30, 60, 70, 120, 180, 1,320, and 2,760 minutes after infusion. A 0.5 ml-aliquot of the 111 In-MAb solution was also obtained to serve as a standard and isotope decay control. Blood samples were centrifuged and duplicate 100-µl aliquots of plasma were added to 13- × 100-mm disposable glass test tubes. We assessed radioactivity by using a model 5360 scintillation gamma counter from Packard Instrument Co. (Downers Grove, IL). Urine samples were collected in 8-hour aliquots over 48 hours following infusion. Total urine volume was measured and duplicate 100-µl aliquots were assayed for "In activity as described above. All analyses were adjusted for isotopic decay; "IIIn measurements in plasma were compared with measurements of murine MAb in serum at similar time points. Values were subjected to nonlinear regression analysis for calculation of standard pharmacokinetic parameters.

RESULTS at a 1 11 12 to 2 drive beautiff as w dAM belgins

Toxicity and Sensitivity of Imaging With ZME-018

We observed no short- or long-term side effects in any patient regardless of MAb dose received, nor were any allergic symptoms such as fever, chills, rash, or anaphylac-

Krejearck and Dicker (10). Prior to use

tic reactions seen. Likewise, there were no significant changes in hematologic parameters and liver or renal function tests.

The total number as well as the percentage of metastases that imaged at escalating doses of ZME-018 are shown in table 1. Of a total of 171 metastases which had been previously diagnosed by conventional techniques, 110 were visualized for an overall positive imaging rate of 64%. Optimum imaging was seen at MAb doses above 2.5 mg. For example, only 8 of 28 metastases were imaged at MAb doses less than 5 mg, compared with 102 of 143 metastases imaged at antibody doses of 5 mg and above (P<.005, chi square). There were no significant differences in imaging efficiency between 5, 10, and 20 mg antibody. A plateau in imaging efficacy was observed at 40 mg. Hence optimal imaging was noted at doses between 5 and 20 mg MAb and at specific activities of ¹¹¹In between 0.25 and 1 mCi/mg.

In 22 instances, the isotope localized in areas which did not correspond with metastases (table 1). In two instances, it was observed in the left upper quadrant, presumably in the bowel. Radioactivity persisted in these sites up to 6 days after MAb administration. Also, four areas of uptake in bone were not seen on 99 technetium diphosphonate bone scan. Isotope localized in the axillae in 3 patients. In 1, radioactivity in the groin area antedated the appearance of 2 palpable lymph nodes (fig. 1). To date, 4 of 22 sites (18%) seen with MAb have been confirmed by other x-rays or physical examinations (true positives).

Isotope uptake was related to tumor size and disease site. As shown in figure 2, mean tumor size and the percentage of metastases imaged were correlated. The size limit for detection by the gamma scanner was 1 cm; no tumors less than 1 cm in diameter imaged. The number and percentage of skin (65 of 80=81%) and lymph node metastases (19 of 26=73%) were imaged to a greater extent than lung (12 of 24=50%), bone (6 of 15=40%), brain (4 of 8=50%), liver (3 of 10=30%), and adrenal gland (2 of 6=33%).

Indium-111-ZME-018 Distribution and Pharmacokinetics

Representative total body scans of a female patient (No. 20) with multiple soft tissue metastases are shown in figure 3. At 2 hours following infusion, there was rapid distribution of the isotope in the blood pool with nonspecific uptake occurring in her spleen, liver, bone, gastrointestinal tract, and nasopharynx (fig. 3A). In several male

TABLE 1.—Number of metastases imaged in relation to average total dose of MAb and specific activity of 111 administered

Mean dose	Mean specific activity of ¹¹¹ In, mCi/mg	No. of		Metastases	No. of uncorrelated	
MAb, mg			No. imaged	No. known	%	sites of isotope uptake
0.6	8.3	Supplied to the	Anderspn	d M mar 4 mons	25	Case The Orderson of Texas
2.5	2.0	4	7	24	29	Hospital and Tome Tashing
5	1.0	5	6	10	60	Lyorice E lbc., San Diego, I
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d) were gerforme		abdomen, pelvi				Houston, TX 970308
Total		30	110	171	.64	22

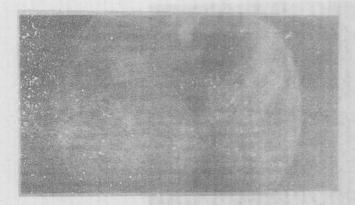


FIGURE 1.—Computer scan of ¹¹¹In-ZME-018 uptake in a patient with a soft tissue mass in the right groin (arrow). This lesion was seen by MAb scan before its discovery on physical examination.

patients studied, testicular uptake was observed (not shown). After 72 hours (fig. 3B), considerable clearance of radioactivity from the blood pool had occurred, although the isotope remained in the liver and spleen. Multiple skin and lymph node metastases could be clearly seen.

A summary of plasma pharmacokinetics of 25 patients who received MAb at doses of 2.5, 5, 10, 20, and 40 mg combined with 5 mCi 111 In is shown in table 2. There was variability in the calculated mean half-life for the various dose levels. A significantly greater (P < .01) plasma half-life was seen in patients receiving 40 mg (2,016.2 \pm 222.7) compared with those receiving 2.5 mg (1,069.9 \pm 127.5). Several patients at each dose level had a short α -phase half-life, followed by a prolonged β -phase. The apparent mean V_d did not vary significantly with dose (range=3.6 \pm 0.5 μ l at the 10-mg dose to 4.6 \pm 0.7 μ l at the 2.5-mg dose). In all instances, the V_d approximated the total plasma volume. The area under the C X t increased from a mean of 483 \pm 72.2 μ Ci/ml \times minutes at 2.5 mg MAb to $1,119.5 \pm 211.9 \ \mu \text{Ci/ml} \times \text{minutes} \ (P < .05) \ \text{at } 40 \ \text{mg}$ MAb. With a moderate increase in C × t, mean clearance from plasma in milliliters per kilogram × minutes decreased significantly with increasing MAb dose (i.e., 0.0591 ± 0.0140 at 2.5 mg to 0.0310 ± 0.003 at 40 mg; P = .05).

The mean urinary excretion of 111 In did not change significantly with respect to dose (table 2) and averaged $11.7 \pm 2.2\%$ over 48 hours for patients receiving 40 mg MAb. Most of the 111 In label was excreted over the first

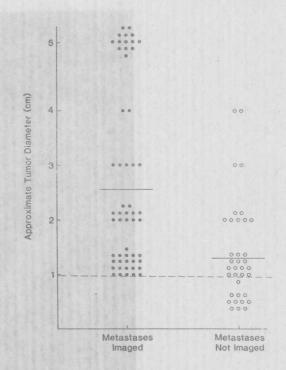


FIGURE 2.—Comparison of size of metastases to uptake of ¹¹¹In-ZME-018. Individual points represent metastases from 25 of 30 patients studied. Metastases imaged were larger than those that did not image (P<.01).

8 hours (5%), with 5.5% being excreted gradually over the next 40 hours.

DISCUSSION

The most significant findings in this study were that ¹¹¹In-ZME-018 was capable of detecting over 70% of previously known metastases at doses of 5 mg and above and that imaging appeared dependent on tumor size and possibly metastatic disease site. Moreover, the biodistribution of MAb and ¹¹¹In correlated with a prolonged in vivo plasma half-life and limited urinary excretion.

The reason for a lower percentage of metastases imaging at the 2.5 mg/5 mCi dose of MAb is unknown. One possibility is that early saturation of nontumor receptor sites such as in spleen and liver occurs, followed by gradual uptake of the MAb by the tumor. Uptake in nonjumor

TABLE 2.—Pharmacokinetic summary of MAb ZME-018

MAb dose,	Mean half-life, min		Mean V _d	Mean C × t.	Mean plasma	Mean 48-hr urinary excretion,
	α-phase	β-phase	liters	μCi/ml × min	clearance ^a	cumulative %
2.5	87.8±19.6	1,069.9±127.5	4.6±0.7	483±72.2	0.059±0.0140	16.7±5.4
5.0		1,470.5±163.6	4.0±0.5	752.2±133.3	0.026±0.002	8.7±0.5
10.0	195.6±183.4	1,648.7±295	3.6±0.5	929.7±217.6	0.0263±0.0038	9.6±0.8
20.0		1,747.8±300.6	4.4±0.4	943.1±196	0.0281±0.006	10.5±1.7
40.0	58.1	2,016.0±222.7	3.8±0.5	1,119.5±211.9	0.0310±0.003	11.7±2.2

^a Plasma clearance values = milliliters/kilograms × minutes.

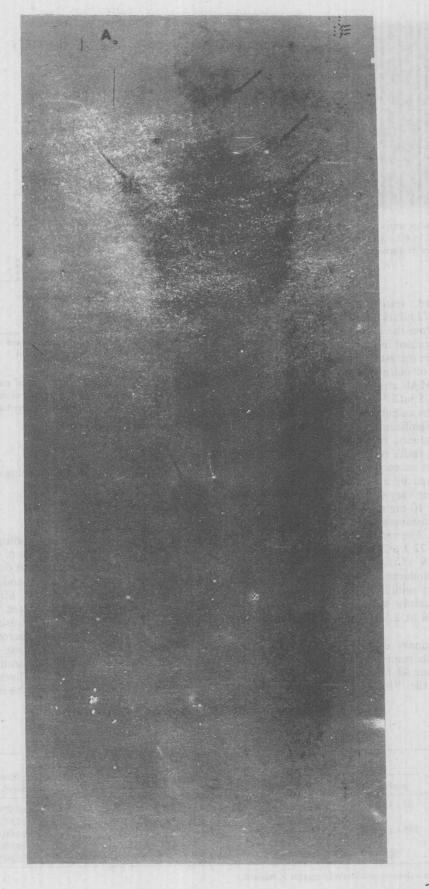




FIGURE 3.—A) Posterior views of a total body scan of a female patient who received 20 mg MAb. *Note* blood pool distribution of isotope with uptake in liver, spleen, nasopharynx, bowel, and bone. Numerous subcutaneous metastases can be seen (arrows). B) Total body scan of same patient at 72 hr. Clearance of isotope from blood pool allows for better detection of tumor (arrows). Considerable isotope remains in liver and spleen.

areas could either be nonspecific, such as by binding of MAb by way of crystallizable fragment receptors (12), or specific, due to low but significant expression of tumorassociated antigens on normal tissues. It is possible that ¹¹¹In alone can localize in liver by binding to transferrin (13).

In 22 instances, the isotope was seen in areas which could not be confirmed as being metastases. At this time, we find it difficult to prove whether these areas are true areas of disease versus false positives due to the difficulty in obtaining biopsies in every case. However, in 1 patient, positive monoclonal scans were seen before the appearance of lymph nodes on physical examination (fig. 1). Likewise, 2 patients had positive areas in bone by MAb scan that were later confirmed by 99 technetium bone scan.

Variables that appeared to have a significant effect on imaging efficiency were tumor size and site of disease. In no instance did a tumor less than 1 cm image. Similar findings were observed by Larson et al. (2) following administration of ¹³¹I-MAb (96.5) Fab fragments which recognize an M_r antigen with a molecular weight of 97,000 (p97), as well as in an earlier study by our group in which melanoma patients received ¹¹¹In-96.5, i.e., whole IgG (6).

Soft tissue sites, such as skin and lymph nodes, were more readily visualized than visceral sites, such as lung, bone, brain, or liver. In most of the patients, liver metastases could not be distinguished from background isotope. In patients No. 2 and 18, "cold" areas were observed corresponding with metastases, similar to what would be observed with 99 technetium per technitate liver scans. However, in 2 patients who received 40 mg MAb, "hot" areas were observed corresponding with tumor sites. Preliminary analyses suggested that the ability to image soft tissue metastases did not always correlate with size (data not shown). Hence other variables, such as heterogeneity of antigen expression, accessibility of antigen to antibody, i.e., brain or proximity of individual lesions to the gamma camera, or both, may play a role in our ability to discriminate metastases from background isotope. Further studies with animal models directed toward confirmation of these hypotheses are needed.

The biodistribution and pharmacokinetics of ZME-018 in man were comparable to those observed with 111 Inanticarcinoembryonic antigen MAb (14), 111 In-antimelanoma MAb to high-molecular-weight, melanoma-associated antigen (240,000) in the nude mouse model (15), and IIIIn-antihepatocarcinoma MAb in the guinea pig (16). In these studies, rapid distribution of isotope in the blood pool was followed by a gradual increase in tumor sites by 48 hours. Considerable radioactivity was observed in liver and spleen as late as 6 days following antibody administration. We reported similar findings when we used ¹¹¹In-MAb 96.5 (6), as did Rainsbury et al. (8) with an "IIIn-MAb reactive with breast carcinoma. The prolonged half-life of 111 In-ZME 018 in the circulation with a diminished excretion of "IIIn over 48 hours could account for the higher background of isotope than that seen with ¹³¹I-labeled antibodies, which have a more rapid half-life and greater urinary excretion due to dehalogenation (9). The pharmacokinetics of ZME-018 in this study differ from that seen in our previous imaging study with antip97 MAb 96.5 (11). In this study, we observed no significant change in the V_d or the clearance of ZME-018 over

time up to 40 mg, whereas the V_d of 96.5 in the previous study dropped significantly at MAb doses above 2 mg. The decrease in V_d corresponded with a gradual increase in C × t. The data suggested that low doses of 96.5 rapidly localized in extravascular sites, i.e., liver, whereas ZME-018 did not. Visually, it appeared that 96.5 had a greater localization in liver than ZME-018, which localized to a greater extent in spleen (data not shown). Although subjective, these findings are important with respect to other clinical trials with MAb. Because both ZME-018 and 96.5 are MAb of the subclass IgG2a, the variation in pharmacokinetics and isotope distribution may be reflective of antigen recognition in vivo rather than differences in MAb structure. Hence the in vivo pharmacokinetics of each mouse MAb studied may be entirely different depending upon the antigen which it recognizes or other unknown parameters.

The nonspecific localization of ¹¹¹In appeared to be the most significant problem in this study and in previous studies. Further technical developments including computer enhancement or subtraction techniques, other imaging agents, or the use of antibody fragments (17) will be necessary before radioimmunoimaging with MAb will become a routine diagnostic tool in clinical medicine. Nevertheless, radioimmunoimaging may serve as a useful adjunct to conventional diagnostic procedures as well as therapy with radiolabeled MAb and MAb-drug conjugates.

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Evaluation of Immunolocalization in Gastrointestinal Cancer

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ABSTRACT—Tumor localization by a ¹³¹I-labeled monoclonal antibody to CEA has been evaluated in a series of 50 patients with clinically suspected primary or recurrent gastrointestinal cancer. Eighty-five percent of the primary tumors were correctly detected, as were 43% of associated nodal metastases. Localization was compared with computerized tomography in the detection of recurrent disease. Each technique correctly identified 61% of the sites but missed 39%. In addition, labeled antibody localization produced a significant number of false-positive images. Radioactivity accumulated by tumors, both primary and secondary, was significantly higher than that in surrounding normal tissue (P < .01). However, < 0.8% of the injected radioactivity and 0.01% of the injected antibody were detectable in the tumors. Radiolabeled antibody was rapidly cleared from the circulation, and this may reflect a recipient reaction to the foreign protein.—NCI Monogr 3:11-17, 1987.

One of the exciting clinical applications of tumor localization by labeled antibodies is the detection of small tumor volumes, which are below the resolution of conventional techniques. Information about the spread of disease before treatment and the early recognition of recurrent disease are both important for the management of the patient with cancer. In two previous studies of gastrointestinal cancer, labeled antibodies to CEA detected 90% (1) and 42% (2) of the tumor sites. The development of monoclonal antibodies (3) has the potential to overcome the limitations of cross-reactivity present in these early studies, which produced such widely differing results. This study has evaluated a monoclonal antibody to CEA in patients with primary and recurrent gastric and colorectal cancer. The results of external scanning have been determined, patients have been carefully monitored for adverse reactions to the labeled preparations, and the distribution of radioactive antibody in the circulation and in the tumors has been investigated.

MATERIALS AND METHODS

Preparation of Labeled Antibody

Monoclonal antibody 11-285-14 is an IgG1 prepared in

ABBREVIATIONS: ELISA = enzyme-linked immunosorbent assay; CT = computerized tomography.

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a collaborative project between the Surgical Immunology Unit of the Queen Elizabeth Hospital and Eli Lilly and Co. by conventional methods using CEA extracted from liver metastases of a colorectal carcinoma (4). Immunohistochemical studies have shown that it binds to CEA in all colorectal cancers tested (5) and 92% of gastric cancers (6). The labeled antibody is preferentially accumulated in colorectal cancer xenografts (7). Approximately 200 µg of antibody solution were labeled with 0.75-1.45 mCi of ¹³¹I by the chloramine-T method (8). Labeled preparations were tested 1) for sterility and the absence of pyrogens prior to administration to patients and 2) for anti-CEA activity by ELISA (9) and by indirect immunoperoxidase staining (10).

Patients

Fifty patients were studied, 24 with primary gastrointestinal cancer and 26 with suspected recurrent disease. The diagnosis of primary disease was made by conventional methods of investigation. There were 11 patients with gastric cancer, 10 with cancer of the colon or rectum, and 3 with primary squamous cell carcinoma of the esophagus. In the 26 patients with suspected recurrent disease, the diagnosis was based either on the development of new susticious symptoms or an elevated serum CEA level. All patients were tested for possible hypersensitivity to the monoclonal antibody by intradermal injection of 10 µg of antibody in normal saline, which was assessed at 30 minutes and again at 24 hours. Potassium iodide (60 mg three times a day) was given 24 hours prior to the administration of the labeled preparation and was continued for a week to block thyroid uptake. Potassium perchlorate (200 mg four times a day) was given in the 24 hours prior to the first scan and was continued until after the second scan had been completed, to block nonspecific uptake by the stomach or salivary glands of the 99mTc-labeled preparations used for subtraction imaging (11).

Labeled antibody infusion was undertaken as an inpatient procedure, and patients were carefully monitored in the first 24 hours for adverse systemic effects. Intravascular distribution of the labeled preparation was assessed by analysis of blood samples taken at 6, 24, 48, and in some cases, 72 hours after infusion. Collections of urine and feces were made for up to three consecutive 24-hour periods.

Gamma Camera Scan

Patients underwent scanning on a CGR Gamma Tome 9000 gamma camera 24 and 48 hours after antibody administration. This camera incorporates a medium-energy collimator with a large field of view. For estimation of the background blood pool activity, 99mTc-labeled pertechne-