Tumor Imaging with I-131 Labeled F(ab')_2 Fragments of Monoclonal Antibodies

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Using radiolabeled F(ab')_2 fragments of monoclonal antibody associated with a noncirculating cell surface antigen of colon carcinoma, we have demonstrated preferential localization in small deposits of human colon carcinoma. (Images show tumor deposition without background subtraction.) Biologic distribution of the F(ab')_2 fragments is also evaluated. In 16 patients studied to date, tumor deposits as small as 1.5 cm have been readily visualized on unprocessed images without background subtraction. Optimal imaging time (tumors best defined) is 72-96 hr postadministration.

Cell fusion techniques have produced monoclonal antibodies specific for single human antigenic determinants (1, 2). We have initiated imaging procedures using the antigen-specific portion of these antibodies, F(ab')_2 fragments labeled with I-131, in patients with colon carcinoma. Optimal imaging procedures are discussed in detail; sensitivity and specificity of the method and biodistribution of I-131 antibody fragments are discussed elsewhere (3).

Materials, Methods, and Procedures

F(ab')_2 fragments of monoclonal antibody 1083-17-1A, an IgG_2 immunoglobulin directed against a colon carcinoma cell surface antigen (Wistar Institute, Philadelphia, PA), are radiolabeled with I-131 (iodogen method) and passed over a sterile, pyrogen-free Sephacryl column to remove free iodine and aggregates of the antibody fragments. This material is then tested for sterility and pyrogenicity, percentage of protein binding by I-131, and relative immunoreactivity (3).

Informed consent is obtained after full discussion of the procedure with the patient. Lugol's solution is given orally for three days prior and ten days after intravenous administration of I-131-labeled antibody fragments to block thyroid uptake of free I-131. After an intravenous catheter is placed in the forearm to permit ready access to a vein in the event of an allergic reaction and to insure the proper route of radiopharmaceutical administration, a skin test is placed using a sample of the antibody fragments to determine hypersensitivity to mouse immunoglobulin. During the intravenous administration of approximately 1 mCi (37 MBq) I-131 associated with 100-300 μg F(ab')_2 fragments, flow images are obtained (4 sec each for 5 min) and an immediate static I-131 image is made. Images are acquired on both film and computer, using a large field scintillation camera with medium energy collimator. (For biodistribution evaluation, not discussed here, blood samples are obtained for determination of clearance rates of total I-131 from blood and protein-bound I-131 from plasma. Two- and 24-hr uptakes by the thyroid are measured.) Static images were obtained at 4, 24, 48, 72, and up to 130 hr postinjection with images centered on areas of known or suspected colon carcinoma, metastatic or primary.

At each imaging session, red blood cells are labeled in vivo (4) with Tc-99m (2 mCi). A Tc-99m image is taken corresponding to each I-131 view—using the dual peak feature of the camera and without the patient being moved—for later use in background subtraction if necessary (3). Images are evaluated both with and without background subtraction. For background subtraction of blood pool activity on the computer (Fig. 1), a region of interest is drawn to outline the heart (reflecting blood pool on the Tc-99m image). This same region of interest is then applied to the corresponding I-131 image and the ratio of counts in these regions of interest is obtained. The images are normalized to equalize the counts in this blood pool region of interest. The resulting Tc-99m image is then subtracted from the corresponding I-131 image to arrive at a blood pool subtraction F(ab')_2 antibody image.

Results and Conclusions

Images demonstrate preferential uptake of I-131-labeled F(ab')_2 fragments by approximately 80% of tumor masses in the size range of 1.5-10 cm. (Tumor size and pathology were confirmed by CT scan and biopsy in most patients.) These tumor sites are readily evident, even in the liver, a route of excretion and therefore high background, without image processing, although background subtraction does improve contrast (Figs. 2 and 3).

The optimal imaging time, based on visual inspection of unprocessed images obtained daily up to 7 days postadministration, has been found to be 72-96 hr (Fig. 4). The same optimal time holds for evaluation of the background-subtracted images. The stomach is visualized (excretion of free I-131) but hepatic and renal activity has been minimal, and activity in these normal routes of excretion has not presented diagnostic difficulties. Activity has not localized in any site other than tumor and these routes of excretion.

We are demonstrating a preferential localization of radio­labeled F(ab')_2 fragments of monoclonal antibody in approximately 80% of large and small deposits of human colon carcinoma. Localized activity in tumor is visualized equally well.
FIG. 2. (A) Right lateral and (B) right anterior oblique liver-spleen images obtained with 4-mCi of Tc-99m sulfur colloid.

FIG. 3. Right lateral and right anterior oblique views of same patient shown in Fig. 1. (A and B). Unprocessed I-131-F(ab')₂ imaging at 72-hr postadministration. (C and D). Corresponding blood pool subtracted images demonstrate some quality enhancement but tumor deposit is easily visualized both with and without background subtraction.

with and without computer enhancement of the images. Optimal imaging time is 72–96 hr postadministration of I-131-F(ab')₂ fragments. This new imaging modality shows promise as a sensitive and specific tumor imaging agent.

FIG. 1. (A). I-131-F(ab')₂ right anterior oblique abdominal image shows areas of increased activity in tumor and stomach. (The latter represents normally excreted activity in the stomach.) (B). Tc-99m labeled red blood cell image of abdomen in right anterior oblique view demonstrates hypovascularity in hepatic metastasis. (Note blood pool activity in the heart.) (C). Cardiac region of interest of fig. 1B. (D). Cardiac region of interest of fig. 1A. (E). Normalized, subtracted right anterior oblique abdominal image demonstrates significant activity only in tumor site and stomach (excreted I-131).

FIG. 4. Posterior abdominal views demonstrate approximately a 5-cm tumor in posterior-superior aspect of right lobe of liver. (A). Liver-spleen scan using 4-mCi of Tc-99m sulfur colloid. (B). 48-hr posterior view of abdomen made with I-131-F(ab')₂ demonstrates tumor in right lobe of liver and also normal routes of excretion, i.e., kidneys and stomach. (C). 72-hr, same as above. (D). 96-hr, same as above. (E). 168-hr, same as above.

References