Radioimmunoscintigraphy of Colorectal Carcinoma Using Technetium-99m-labeled, Totally Human Monoclonal Antibody 88BV59H21-2

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Abstract

Radioimmunoscintigraphy (RIS) using human monoclonal antibodies offers the important clinical advantage of repeated imaging over murine monoclonal antibodies by eliminating the cross-species antibody response. This article reports a Phase I-II clinical trial with Tc-99m-labeled, totally human monoclonal antibody 88BV59H21-2 in patients with colorectal carcinoma.

The study population consisted of 34 patients with colorectal cancer (20 men and 14 women; age range, 44–81 years). Patients were administered 5–10 mg antibody labeled with 21–41 mCi Tc-99m by the i.v. route and imaged at 3–10 and 16–24 h after infusion using planar and single-photon emission computed tomographic (CT) techniques. Pathological confirmation was obtained in 25 patients who underwent surgery. Human antimurine antibody (HAMA) titers were checked prior to and 1 and 3 months after the infusion.

RIS with Tc-99m-labeled 88BV59H21-2 revealed a better detection rate in the abdomen-pelvis region compared with axial CT. The combined use of both modalities increased the sensitivity in both the liver and abdomen-pelvis regions. Ten patients developed mild adverse reactions (chills and fever). No HAMA response was detected in this series.

Tc-99m-labeled human monoclonal antibody 88BV59H21-2 RIS shows promise as a useful diagnostic modality in patients with colorectal cancer. RIS alone or in combination with CT is more sensitive than CT in detecting tumor within the abdomen and pelvis. Repeated RIS studies may be possible, due to the lack of a HAMA response.

Introduction

Since the development of hybridoma technology, significant improvements have occurred in the production of monoclonal antibodies used for both diagnostic and therapeutic purposes. A variety of well-characterized murine antibodies directed against tumor-associated antigens have been used in the radioimmunoimaging of tumors. Concerns exist regarding the development of HAMA following the administration of these radioimmunoconjugates, because the routine application in clinical practice may require repeated injections. HAMA response causes rapid binding of the radiolabeled antibody in the circulation, resulting in low or no targeting of the tumor. Several improvements have occurred in the production of monoclonal antibodies by eliminating the cross-species antibody response.

Materials and Methods

Radio labeling and Quality Control. 88BV59H21-2 was radiolabeled with Tc-99m (sodium pertechnetate) using stannous chloride and saccharic acid (6). The amount of the antibody ranged from 5.4 to 10 mg. The Tc-99m dose was 21–41 mCi. The final solution demonstrated a high labeling efficiency, as measured by TLC. The protein-bound fraction ranged from 94.1 to 99.9%. In all cases, the endotoxin concentration in the radioimmunoconjugate preparation was less than 2 EU/ml, as determined by the Limulus Amebocyte Lysate assay.

Patients and Study Protocol. The study was designed as a Phase I-II clinical trial to determine the safety and efficacy of the Tc-99m-labeled 88BV59H21-2 monoclonal antibody as a radioimmunoscintigraphic agent in colorectal carcinoma. Eleven patients in this group were also studied under a different protocol evaluating the intraoperative use of a γ detection probe (7).

This prospective, open-label trial included patients with histologically proven colorectal cancer, with at least one documented site of tumor involvement by conventional diagnostic techniques or suspected metastatic disease on the basis of elevated carcinoembryonic antigen. Thirty-four patients (20 men and 14 women ages 44–81 years) were entered into the study. Twenty-five patients underwent surgery. Eligibility criteria included a minimum age of 18 years, a Karnofsky performance status of 70 or greater, and serum bilirubin and creatinine levels of less than 2.0 mg/dl. Additional inclusion criteria required the patients to be off any cytotoxic therapy, to have no signs of residual toxicity, and to have not received other antibody infusions for at least 2 weeks preceding the infusion of 88BV59H21-2. Patients who were pregnant or lactating, those with a history of other primary malignancy (except in situ carcinomas or nonmelanoma skin cancer), and those with neurological disease were excluded. The protocol was approved by the University of Miami Institutional Review Board, and prior written informed consent was obtained from all patients.

Baseline evaluation included history and physical examination, complete blood count with differential, serum electrolytes, renal and hepatic function tests, carcinoembryonic antigen, and urinalysis. Preoperative electrocardiograms and chest films were obtained routinely, and all patients had CT of the liver, abdomen, and pelvis within 4 weeks preceding antibody infusion. Serum samples for HAMA were also obtained prior to infusion and at 1 and 3 months after infusion. The detection of HAMA was performed using ELISA. The assay was designed to measure antidiotype and antiantibody reactivity against the 88BV59H21-2 antibody with a limit of sensitivity of 50 ng/ml.

All patients were initially given i.v. doses of 300 mg antibody and were observed for possible allergic reactions. The patients were then infused i.v. over a 15–30-min period. Vital signs were measured prior to infusion and monitored closely for 2 h thereafter. Radioimmunoscintigraphy was performed at 3–10 and 16–24 h after infusion of the radioimmunoconjugate. Planar images were acquired using a large-field-of-view camera with a parallel-hole low-energy all-purpose collimator, using a 20% window centered at 140 KeV. Single-photon emission CT of the liver, abdomen, and pelvis was obtained using a matrix size of 64 × 64, a 360° orbit, 40-s acquisitions, and sampling every 6°. Images were reconstructed using a filtered back-projection algorithm.
The combined use of CT and RIS increased the sensitivity rate to 100% in the liver (Table 4).

Discussion

Tc-99m-labeled 88BV59H21-2 is one of the first monoclonal antibodies of human origin used for imaging of colorectal cancer. The results of our Phase I-II trial demonstrated a significant advantage of 88BV59H21-2 over murine whole antibodies from the standpoint of immunogenicity. No HAHA response was noted in any of the 34 patients studied. Repeated injection, therefore, is possible without interference with tumor targeting.

CT is not very sensitive in detecting transcoelomic disease. It is somewhat better in the detection of pelvic tumor. Our results showed that the Tc-99m-labeled 88BV59H21-2 is most useful in detecting abdominal and pelvic lesions, with a sensitivity rate of 75%, whereas the sensitivity rate of CT is 52%. The combined use of both modalities increased the sensitivity to 84%. CT seems to be superior to RIS with 88BV59H21-2 in detecting liver metastases. Earlier studies with other radioimmunoconjugates have found that RIS is complementary to CT for imaging of liver lesions (8). Liver lesions appear frequently as photopenic lesions. It may be argued that such a pattern cannot be counted as true positive, because this does not reflect specific tumor targeting with the antibody. However, photopenic lesions do not represent primary failure of tumor antigen-antibody binding necessarily. Nonspecific accumulation of radioactivity in the liver, large tumor size, increased intratumoral pressure, tumor necrosis, and other delivery problems all contribute to this phenomenon. From the clinical point of view, demonstration of the liver lesions by either radioimmunotargeting or nonspecific means could be considered equally relevant. False-positive localization occurred mostly in the delayed abdominal images, due mainly to late excretion of radioactivity in the large bowel, with some possible contribution of reconstruction artifacts on single-photon emission CT.

The adverse effects have been limited to short-lived and low-grade fever and chills, due possibly to very low level cytokine activity, which was eliminated subsequently by the current antibody purification technique.

A standard laparotomy was performed, in which all abdominal organs, peritoneal surfaces, and major lymph node groups were visualized and palpated, in addition to the known primary and/or metastatic lesions. All visible lesions with the exception of one suspected liver metastasis were biopsied. The imaging characteristics of CT, RIS, and the combination of CT and RIS (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) were calculated using pathology as the standard. Analyses were performed by individual lesion and by anatomical region (liver, abdomen, or pelvis).

Results

Adverse Reactions. Ten patients developed grade I-II fever and/or chills. There was one incident of mild abdominal pain and one mild hyperventilation. All events were self-limited and resolved without any sequelae. The febrile reaction was not endotoxin related but was likely due to a contaminant cytokine, which was eliminated subsequently by a modification of the antibody purification scheme.

HAHA Results. No HAHA reactivity was found in any patient at any time point after the administration of the antibody.

Imaging Characteristics. The blood pool, liver, spleen, and kidneys were visualized normally in both early and delayed images. The blood pool was reduced considerably in delayed images. Delayed images showed occasional colonic uptake, which was most likely to be intraluminal in origin. Liver lesions appeared as photopenic lesions in early images and showed some degree of filling in the delayed images. Sizes of the detected lesions ranged from 1 to 5 cm.

Analysis by lesion in the abdomen and pelvis revealed a higher detection rate with RIS than with CT. Sensitivity rates were 52, 75, and 84% for CT, RIS, and CT plus RIS, respectively. Specificity rates, in the same order, were 93, 83, and 76%, respectively (Table 1). Analysis by lesion in the liver revealed a better sensitivity with CT than with RIS. The combined use of CT and RIS revealed a sensitivity rate of 85% (Table 2).

Analysis by region also revealed a better detection rate with RIS in the abdomen-pelvis region. The sensitivity rate was 86% with RIS alone and 71% with CT alone. The combined use of both modalities increased the sensitivity to 95%. Specificity was higher with CT (Table 3). Analysis by anatomic region in the liver revealed equal sensitivity for CT and RIS. The combined use of CT and RIS increased the sensitivity rate to 100% in the liver (Table 4).

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Tc-99m-labeled 88BV59H21–2 RIS shows promise as a new diagnostic modality in the investigation of patients with colorectal cancer. RIS complements conventional diagnostic modalities by virtue of its superior sensitivity in detecting extrahepatic abdominal and pelvic tumors and the functional rather than anatomical basis of imaging. The radiopharmaceutical is easy to prepare and deliver. Absence of immunogenicity may permit repeated use in patients at high risk for recurrence.

References
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