Radioimmunodetection of Colorectal Carcinoma

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Introduction

The application of radioimmunoscopyntigraphy (RIS) in colorectal carcinoma is limited to the search for recurrent disease in patients in whom aggressive palliative or salvage treatment is contemplated. Its role, if any, in the staging of primary colorectal carcinoma awaits clinical studies that would demonstrate benefit to patients from treatment of occult disease detected by RIS alone.

111-indium-saturnomab pendetide (111-In-CYT-103, OncoScint CR/OV, Cytogen Corp, Princeton, NJ) is the currently approved radioimmunoscyntigraphic agent for imaging colorectal (and ovarian) carcinoma. Saturnomab pendetide is a conjugate of a chelator (DTPA) and a monoclonal murine antibody (MAb-B27-3) specific for a tumor-associated glycoprotein (TAG-72) frequently expressed by colorectal and ovarian carcinomas. The TAG-72 antigen is not restricted to these malignancies, and antibody labeling regularly occurs in salivary glands, postovulatory endometrium, and benign ovarian tumors.

MAb-72 is an intact antibody. The 111-indium label, bound by the chelator, provides the best match of radiolabel half-life to antibody clearance for resolution of lesional uptake from the substantial background activity. Nonspecific background uptake is so pronounced in the liver that approval of the agent by the Food and Drug Administration is for detection of “extrahepatic” spread of colorectal and ovarian tumors. Nonspecific uptake also is substantial in spleen and bone marrow as well as gastrointestinal and genitourinary systems. Focal nonspecific uptake is seen in colostomies, aneurysms, adhesions, and areas of inflammation, particularly diseased joints.

Application of 111-In-CYT-103

Although uncommon, isolated recurrences of colorectal carcinoma in the liver, pelvis, abdomen, or lung are resectable for cure in up to 20% of presentations, with a substantial minority of such patients experiencing long-term palliation or cure.1-4 Doerr et al[5] reported on their use of 111-In-CYT-103 in 19 of these patients. All had undergone conventional workup for suspected recurrence, including physical examination, computed tomography (CT) studies and carcinoembryonic antigen (CEA) blood testing. Based on the preoperative evaluation, four were believed to have locoregional recurrence and six to have liver recurrence. Nine patients had CEA elevation as the sole evidence of recurrent disease. Of these nine, monoclonal antibody imaging correctly identified the site of recurrence in six patients (Fig 1). All extrahepatic abdominal and pelvic recurrences found at surgery were located preoperatively by monoclonal antibody radioimmunoscyntigraphy. The sensitivity of CT for these lesions was only 43%. The authors reported that radioimmunoscyntigraphy influenced clinical management in 55% of the patients.

The same group has compared the sensitivity of 111-In-CYT-103 and CT in a larger group of preoperative patients with primary and recurrent colorectal carcinoma and found the sensitivity and accuracy of monoclonal radioimmunoscyntigraphy to be approximately 70% in both extrahepatic abdomen and pelvis.[6,7] For extrahepatic abdominal disease, this was twice the sensitivity obtained by CT and reflected the capacity to detect peritoneal tumor sites as well as tumor within normal-sized lymph nodes. The authors found monoclonal antibodies within the pelvis to be particularly effective for distinguishing between recurrent tumor and postoperative or postradiation scarring (Fig 2).

Overall, this modality alone was responsible for detecting disease sites in 10% of their patients. Results such as these, as well as the advantage of whole-body imaging, have led some authorities to recommend 111-In-CYT-103 imaging, following chest radiographs and abdominopelvic CT, as standard for the evaluation of suspected recurrent colorectal carcinoma.[8]

Limitations

Enthusiasm for this modality should be tempered, however, by an appreciation of the still limited data on the clinical impact of its use.[9] Both false-positive and false-negative studies are seen in more than 10% of patients.[10] Although the sensitivity of the test depends on the density of TAG-72 antigen expression of the particular tumor deposit, no current in vivo method is available for measuring this variable.[11] In addition, administration of the agent can induce human anti-mouse antibody (HAMA) production. The presence of HAMA reduces the sensitivity of repeat studies and may confound the reliability of unrelated serologic tests that use murine antibodies. In addition, the risk of allergic reactions is introduced. Abdel-Nabi and colleagues[12] observed allergic reactions in 16% of patients undergoing repeat studies.

The use of 111-In-CYT-103 in the initial staging of primary colorectal carcinoma has been examined in a study of 23 primary colorectal carcinoma patients with preoperative radioimmunoscyntigraphy in addition to standard workup.[13] Of the 23 primary lesions, 16 were detected with planar imaging and 21 were detected with single-photon emission computed tomography (SPECT). Five patients were found at surgery to have regional adenopathy, and three of these were detected preoperatively on SPECT images. Unfortunately, false-positive scans were reported for both planar and SPECT techniques. In weighing these uncertainties as well as the cost of the procedure, Ryan[14] has suggested that 111-In-CYT-103 imaging be reserved for patients with particularly aggressive but apparently localized tumors or for patients with indeterminate findings on standard initial staging in whom the surgical or adjuvant chemotherapeutic approach might be altered if metastasis were known to be present.

The appeal of a more direct radioimmunologic approach, using monoclonal antibody raised against CEA to locate recurrent deposits in patients with elevated CEA blood levels, has not been lost on investigators. To date, however, none of these agents has been released for routine clinical use in the United States. Patt et al[15] reported a comparison of two different anti-CEA monoclonal antibodies: a whole antibody (ZCE-025, Hybritech, San Diego, Calif) and a Fab’ fragment (Immuno-4, Immunomedics, Morris Plains, NJ). The latter antibody, being only fragmentary, is labeled with 99m-Tc (99m-Tc); its short half-life and predominant renal clearance should improve the identification of liver lesions. The absence of the highly antigenic Fc region should minimize production of HAMA. Their results in a small group of patients showed no dramatic difference in performance between the two monoclonal antibody preparations. Each obtained true positive studies in the majority of patients as well as false positives in a small proportion.

The overall results were similar to those reported for 111-In-CYT-103.

Radioimmunoguided Surgery

No discussion of radioimmunoscyntigraphy for colorectal carcinoma can close without acknowledgment of the intriguing but as yet unproved adaptation of radioimmunoguided surgery (RIGS).[16] In this technique, a hand-held probe is used intraoperatively to identify areas of increased uptake, some of which would presumably be invaluable otherwise. Encouraging claims for sensitivity for subclinical lymph node metastasis have been made.[17] In one small multi-institutional study of patients undergoing surgery for recurrent colorectal cancer, the positive predictive value of RIGS was 78%. Thirty clinically normal sites in 28 patients were found to contain occult cancer.[18] This issue is discussed in more detail in another article in this issue.[19]

References


