IMMUNOLYMPHSCINTIGRAPHY WITH BCD-F9 MONOCLONAL ANTIBODY AND ITS F(ab')\textsubscript{2} FRAGMENTS FOR THE PREOPERATIVE STAGING OF BREAST CANCERS

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ABSTRACT

In breast cancer, assessment of axillary lymph node status is the most important prognostic factor for accurate staging, management and follow-up of patients with primary tumors. Several studies suggest that preoperative staging with techniques as direct breast lymphography, ultrasound and CT-scan often fail to identify the extent of the metastatic involvement in the axilla. To this end, we have developed a novel, simple, non-invasive and reliable immunolymphscintigraphic (ILS) technique that allows the accurate preoperative diagnosis of lymph node metastasis in patients with early stages of breast cancer\textsuperscript{1-6}. In this article, we report on a consecutive series of thirty-nine breast cancer patients undergoing preoperative staging by ILS using the BCD-F9 monoclonal antibody or its F(ab')\textsubscript{2} fragments. Each patient received 1 mg of a purified preparation containing 1 mCi of Iodine-123, by a subcutaneous injection into the fingerwebs between the 2nd and 3rd finger of both hands. Scans obtained 4, 8 and 12 hours after injection demonstrated adequate tumor accumulation of radiolabeled antibody and accurate tumor visualisation without any background substraction. ILS results were always compared to the histopathological staging. When intact immunoglobulin molecules were injected, 10 out of 11 patients with breast cancer were true positives and 19 out of 21 were true negatives. For the F(ab')\textsubscript{2} fragments, ILS results were positive in 3 out of 3 patients with metastatic cancer and negative in 3 out of 4 patients without metastatic involvement of the axilla. Most importantly to our study, all of the 12 patients with benign breast disease studied showed no positive imaging.
INTRODUCTION

Although the feasibility of radiolabeling antibodies and the demonstration by external scanning that such antibodies localize in target organs was demonstrated 40 years ago, it was undoubtedly the advent of the hybridoma technology and the development of monoclonal antibodies (MAbs) of well-defined specificity, low cross-reactivity, and high affinity to human tumor-associated antigens that has rekindled interest in immunoscintigraphy and allowed the development of a panel of potentially useful tumor markers. Actually, radioimmunodetection of tumors has become the subject of intense research efforts and clinical trials have demonstrated that MAbs can be administered quite safely and will localize specifically to carcinomas, melanomas and human lymphomas. But immunoscintigraphy is still at an early developmental stage and it rarely discloses neoplasms of diameters smaller than 1.0 cm. Recent data have shown that this technique can complement more conventional radiologic techniques and can even detect, in some cases, occult distant metastasis.

We have focussed our studies on the BCD-F9 monoclonal antibody as it appears to meet all the criteria of a useful marker for the radioimmunodetection of axillary lymph node metastasis in breast cancer patients. BCD-F9 is a murine IgG2a monoclonal antibody which was generated by the hyperimmunization of mice with a preparation of whole BT-20 breast carcinoma cells. This antibody identifies a novel human breast associated cell surface antigen: gp39. Using fresh frozen human tissues, we have previously reported that this antigen is present in 69% of the mammary adenocarcinomas studied and 51% of their metastatic tumors. In benign breast lesions, 75% of the fibrocystic diseases and the fibroadenomas studied were positive. In normal tissues, positive staining was mainly confined to the mammary cells, the only two exceptions being the smooth muscle cells surrounding blood vessels and basement membranes lining few epithelia. All the organs of the gastrointestinal, the respiratory, and the genitourinary systems studied were negative, except for a moderate to very low reactivity with the glandular epithelium of the oesophagus and the larynx. Of the 34 non-mammary human neoplasms of epithelial origin studied, only hepatocarcinomas (4/4) were strongly positive while ovarian adenocarcinomas (3/4) were focally positive. Unlike another anti-breast cancer MAb already described, BCD-F9 does not bind to any subset of circulating lymphocytes, leucocytes, erythrocytes or any sarcomas and lymphomas.

We have selected Iodine-123 as the radionuclide to test the feasibility of using our MAb for radioimaging mainly because we believe that I-123 is the best gamma-emitting radioisotope presently available. Its energy of 129 keV is perfectly suited for imaging with a gamma camera. Although its half-life of 13 hours is quite short, I-123 represents an optimal tracer especially when it is coupled to the smaller F(ab') or F(ab')2 antibody fragments which penetrate more easily into the tumor and are rapidly cleared from the circulation. In this paper we present results obtained when I-123 labeled-BCD-F9 was administered subcutaneously to 39 patients with a suspected diagnosis of breast cancer. We also compare the use of F(ab')2 fragments to the intact antibody molecule.

PATIENTS AND METHODS

Patients

A series of 39 patients with either suspected malignant or benign breast lesions were investigated by immunolymphscintigraphy (ILS) a