Radio-Immunoguided Surgery for Large Bowel Cancer

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ABSTRACT

The intra-operative detection of metastatic disease in colorectal cancer depends on tumor-associated antigen and antibodies as well as detection technology. A hand-held gamma detecting probe is capable of detecting as few as 6x10^7 labelled cells in vitro.

In a multicentre phase I-II study using B72.3 with 125I 105 patients (26 primary, 72 recurrent, 6 no tumor) were enrolled. There was 78% localization - 24/32 primary tumors 126/199 recurrent sites. Occult tumor was detected in 30 sites in 26 patients. There was an impact on management in approximately 1/3 of recurrent cases.

Of 17 patients for complete excision of recurrent tumor, 10 had complete excision and 7 recurred in 1 year. Four with elevated CEA had no tumor found, 2 had widespread metastases (no resection), 1 had bilateral radio uptake and biopsy - negative tumor-free at 3 years.

A current Phase II study is being conducted using MoAle CC49 labelled with 1-2Mci with primary tumor localization 86% and 97% in second look metastases.

DISCUSSION

The use of monoclonal antibodies in surgery is founded on the work of Kohler and Milstein who described a technique to produce monoclonal antibodies in 1975. It is hoped the development of monoclonal antibodies to the epitopes of tumor cells will enable investigation of the cellular elements of tumors, improved detection and therapy of cancer. Antibodies to various tumors have been produced. These are, however, not tumor specific. Antigens from tumor cells may be from the cytoplasm or the cell surfaces, and may be found in normal cells of a number of different tissues. The antigens do occur in higher concentration in neoplastic cells than normal cells. This allows quantification and differentiation of cells. The hybridoma technique allows the production of isolated antibodies to specific antigens.

Gold and Freedman isolated carcinoembryonic antigen in 1965. CEA is found in large bowel cancer and since it was isolated, numerous studies using antibodies to CEA have been reported. Hundreds of monoclonal antibodies to neoplasms have been identified and the number of potential antibodies is probably unlimited. As tumor-associated antigens occur on normal cells, the successful application of antibody techniques will depend on the selection of antigens that occur in much larger quantities on tumor cells than normal cells. Neoplastic cells are heterogeneous. This creates problems in selecting antibodies within the same tumor and results in problems in detection and therapy of metastatic lesions. Poste, et al. have shown in a mouse model using an uncloned melanoma line that some of the metastases had different metastatic properties from the original neoplasm.

When an antibody is labelled, the immunoreactivity must not be destroyed. Advantages and disadvantages exist for different isotopes. Iodine is distributed evenly, but deiodination of the antibody may take place as it is sequestered in the thyroid or attaches to other circulating proteins. Indium is more stable, but is selectively concentrated in the liver, making it unsuitable...
for the detection of hepatic metastases. There are also questions relating to the use of whole tumor-associated antigens or fragments of IgG. One might anticipate that molecules of a larger molecular weight might be less permeable to the vascular wall and have more difficulty reaching the receptor sites. Fragments of immunoglobulin are smaller than whole IgG and there is indirect evidence that antibody fragments localize in tumor in greater numbers than the whole immunoglobulin. This may be due to the finding of O'Connor and Bale that the neoangiowality of tumor is more permeable than normal vessel walls.

Murine monoclonal antibodies used in colorectal cancer are anti-CEA, B72.3 19.9, 17.1A, SP-25, 79 T7/36, 250 - 30.6. All have varying capabilities of identifying colon cancers dependent on their individual characteristics. 17-1A antibodies are specific for membrane-bound antibodies while anti-CEA antigen and B72.3 detect colon cancer and shed antigen in the blood stream. The clinical use of radio-immunoguided surgery is a new field which was first described in an experimental model in a nude mouse. Following this, in early clinical studies, colon cancer not identified by conventional means of detection was found in 18% of patients. Using immunohistochemical assays and radio-immunoassays, monoclonal antibody B72.3 identified 80% of colon cancers. The monoclonal antibody is not specific, reacting with ovarian, breast and other gastrointestinal cancers to varying degrees. The in vitro studies were consistent with clinical data generated in intra-operative studies by Martin, et al.

The ability to detect radiolabelled isotopes intraproactively is provided by hand-held devices which have auditory and visual signals. Aitken, et al. described its successful experimental use and a case report in 1984. The probe is hand-held and easily directed to tumors or suspicious areas and placed in close proximity to the tumor. The ability to be as close as possible is important when one considers the inverse square law which is important in measuring the intensity of radiation detected from a small source of radiation. The design of the detector and the inverse square law allow detection of these small sources against the presence of circulating isotope in the background. The ability to bring the probe within a few millimeters of the source allows high ratios of source to background to be achieved.

Important in the consideration of intra-operative scanning with a hand-held gamma probe is the isotope used. The isotope chosen is different from that used for external imaging. The radiation emitted from the high energy isotopes is used in external imaging is very penetrating, and the hand-held gamma detecting probe cannot accommodate detector crystals sufficiently thick to be efficient. The hand-held probe has a small detector and will register a low energy isotope more efficiently. I is a low energy isotope that has several advantages. It has a comparatively long half-life (60 days) and has a tissue half-length of approximately 2.5 cm. Emissions from the background are absorbed in layers of tissue which helps to improve tumor to background ratio. The longer half-life allows the clinician to wait longer until the background levels are excreted to improve tumor-to-background ratios. This makes the assumption that the antibody-isotope conjugate remains attached to the tumor or is lost at a slower rate than circulating conjugate. Clinically this is apparent. The optimum time between injection and probing is influenced by the type of monoclonal antibody and fragments. Circulating immune complexes and antigen shedding from the tumor cell surface may be variables that alter the time.

The monoclonal antibody B72.3 with I as the radionuclide is now being investigated. B72.3 has been studied in tissue sections, nude mouse xenografts and patients. The antibody is an IgG subclass and recognizes mucin glycoprotein TAG-72. I is a weak gamma-emitting isotope, with a 60-day half-life suitable for use with the Neoprobe unit with its sophisticated microprocessor that eliminates background counts. The system has been evaluated in phase I/II and Phase III studies. I mgm of B72.3 combined with 2 mCi of I has been shown to be relatively non-toxic. The mechanism used in clinical studies has been to obtain baseline evaluations, including history and physical examination as for any large bowel cancer. CBC, CEA and coagulation studies and T3 uptakes and TSH are documented. Because of the use of I, SSKI is administered to block the thyroid gland. It is given 10 drops bid for 2 days prior to the injection of I B72.3 monoclonal antibody.