9. Development of an Effective Antibody System for Imaging and Treating Lymphoma

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Cancer is the second leading cause of death in the United States today. Targeting of cancer with molecules has been a goal of medicine for most of this century. Antitumor antibodies can be used to carry radionuclides to tumors for *in vivo* diagnosis and treatment of cancer. Studies of radiolabeled antibodies were initiated in animals by Pressman. He demonstrated that a greater amount of radioactivity accumulated in osteogenic sarcoma of rats when radiodiode was attached to an antibody immunospecific for the sarcoma rather than to a non-immunospecific antiserum. Bale and Spar extended this approach to targeting fibrin in tumors with antibodies in animals and patients. These polyclonal antibodies were not widely applied because immunologic methods, including antibody production, were too primitive to produce antitumor antibodies in the quantity and quality needed for clinical application. This situation was profoundly altered by the development of monoclonal antibody hybridization techniques by Kohler and Milstein. Now, for the first time, large quantities of radiolabeled antibodies that have a single antigenic (epitopic) reactivity and for which good quality preparations can be reliably reproduced, are available. Monoclonal antibody reagents have virtually replaced the heterosera of earlier days. When suitably radiolabeled, these antibodies provide a profound potential for imaging and treatment of cancer. Preliminary clinical trials have demonstrated the feasibility, but also the complexity, of these methods. Order and Larson have demonstrated palliation and objective reduction of tumor volume after administration of radiolabeled antibodies without irreversible damage to other tissues. However, several patients developed transient thrombocytopenia. Furthermore, estimates of the dose of radiation to the liver revealed that this was substantial although tolerable.

Optimization of radioimmunodiagnosis and therapy depends upon selection of a suitable radionuclide, antibody-antigen system, and conditions for administration of the antibody. In addition, optimization of radioimmunotherapy depends upon a foreknowledge of the pharmacokinetics of the radiolabeled antibody, and of the radiation dose distributions. Because existing cancer antigens are located on the cell membrane, and because of nonuniform expression of these antigens on the cells, radionuclides with ionizing emissions of longer range are preferable for treating solid tumors. Radionuclides, such as I-131, Cu-67, and Y-90, provide beta emissions suitable for radiation over longer ranges.

While the ultimate objective is the selection of an antibody antigen system exclusive to the cancer cells, a small amount of crossreactivity with other tissues can be tolerated if there are substantial differences in the amounts or availability of antigen in the cancer when compared to other tissues. Preliminary evaluation of the antibody, radionuclide and radiochemistry can be conducted in mice, but the patient is the final arbiter of the usefulness of a radiolabeled antibody.

We demonstrated that Lym-1, an IgG2a monoclonal antibody produced against tissue from a patient with Burkitt’s B cell lymphoma, accumulated in this tumor when implanted in athymic mice, whether the antibody was labeled with I-131, In-111 or Cu-67. These tumors in mice could be cured when treated with I-131 Lym-1. A foreknowledge of the pharmacokinetics of the radiolabeled antibody can be acquired by established tracer techniques. These tracer techniques can now be implemented in a quantitative manner in patients by scintillation camera imaging. Because single photon emission tomography provides inherently better contrast resolution than conventional scintillation camera imaging, it appears to be the method of choice for treatment planning with radiolabeled antibodies. Sites of B cell lymphoma in patients could be imaged with Lym-1 antibody or its FAb fragment whether labeled with I-131 or In-111. Our experience indicates that at least 5–20 mg of mouse monoclonal antibody must be administered to a patient for optimal accumulation in the cancer. Lesser amounts of antibody are rapidly cleared from the blood by the liver where catabolism occurs. This relates to the existence of anti-mouse Fc receptor sites, which are present in the liver of patients. Under these conditions we have treated 10 patients with fractional doses of I-131 (30–60 mCi) attached to Lym-1. Seven patients demonstrated objective evidence of reduced tumor volume and/or circulating malignant cells. Toxicity has
been low despite total amounts of antibody as great as 97 mg and of I-131 as great as 300 mCi.

In summary, it is possible for the first time to detect, locate, characterize and destroy lymphomatous tissue throughout the body using radionuclide labeled monoclonal antibodies. Scintillation imaging, particularly with emission tomography, provides the opportunity to obtain radiation dosimetry and perform treatment planning using tracer techniques with little risk to the patient.