Radioimmunotherapy for Colorectal Cancer

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Monoclonal antibodies, selected for their ability to recognize and bind tumor-specific antigens, are a promising vehicle for systemic antitumor therapy. Radioimmunotherapy utilizes radioisotopes conjugated to monoclonal antibodies to deliver tumoricidal radiation doses. In the >20 years since radioimmunotherapy began, many obstacles to successful application of this antitumor modality have been overcome. Important contributions include the production of humanized monoclonal antibodies to avoid agent immunogenicity and the use of hematopoietic growth factors to alleviate marrow toxicity. At present, two anti-CD20 agents, Bexar (131I-tositumomab) and Zevalin (90Y-ibritumomab), have been approved by the Food and Drug Administration for treatment of non-Hodgkin’s lymphoma.

The antitumor efficacy of radioimmunotherapy requires a specific interaction between radiolabeled antibody and a tumor cell that persists long enough to deliver a tumoricidal radiation dose. Radioimmunotherapy is a highly effective therapy for hematologic malignancies, with overall response rates ranging from 30% to 85% and efficacy even in chemoresistant disease (1). Unfortunately, similar results have not been achieved for solid tumors, despite extensive study in phase I and II dose escalation trials of patients with colorectal, breast, medullary thyroid, and ovarian cancer (2). Several important differences between hematopoietic and solid tumors may contribute to the relatively poor response of solid tumors to radioimmunotherapy. Compared to lymphomas, solid tumor malignancies are frequently more heterogeneous with respect to antigen expression and density. Agent delivery can also be hampered by large tumor size, location in solid organs or on peritoneal surfaces, limited tumor vascularity, reduced tumor immunogenicity, or rapid cell proliferation, which are all common characteristics of solid tumors. Finally, and most important, solid tumors are less sensitive to radiation, magnifying problems associated with heterogeneity of dose deposition.

Radioimmunotherapy has yet to show significant efficacy in treatment of colorectal cancer. The principal antibodies studied thus far are directed against the shed antigens, carcinoembryonic antigen and tumor-associated glycoprotein 72, or the transmembrane A33 antigen. Most study cohorts were composed of patients with advanced metastatic disease who failed chemotherapy, thereby presenting a difficult population for identification of therapeutic response. Few solid tumor studies have examined the effect of radioimmunotherapy on minimal residual disease. In a phase II study of small-volume colorectal cancer metastases, defined as lesions ≤3 cm, patients treated with the anti-carinoembryonic antigen agent 131I-hMN-14 achieved an objective response rate of 16% and an overall response rate of 58% (3). This study suggests that radioimmunotherapy may prove effective in the adjuvant setting, although more definitive clinical studies have not been reported.

Results presented in this issue by Scott et al. (4) and Chong et al. (5) indicate that 131I-huA33 has many of the characteristics required for antitumor efficacy. Radioimmunotherapy is optimal under conditions of uniformly high antibody uptake in tumor relative to normal tissues. Contrary to most studies of radioimmunotherapy in solid tumors, Scott et al. found that 131I-huA33 was evenly distributed in even large tumors after a single dose (90% of tumor cells by immunohistochemistry) with tumor-to-normal tissue ratios of 1.1:14.5 (median 5.6). Autoradiography documented penetrance of 131I-huA33 to the central portion of metastatic lesions removed at surgery. Exposure time in the normal colonic mucosa was minimal.

Although these studies show success in overcoming heterogeneity of agent uptake and distribution within large tumor masses, a more difficult challenge is the delivery of an optimal tumoricidal dose without prohibitive toxicity. Bone marrow toxicity is the dose-limiting side effect of radioimmunotherapy, occurring at doses of 120 to 200 cGy. Results from phase I and II trials in solid tumors show that hematopoietic toxicity limits radioimmunotherapy delivery to mean tumor doses of 800 to 1,800 cGy, although some patients reportedly achieved tumor doses as high as 6,000 to 7,000 cGy following a single injection (2). In their phase I trial of 131I-huA33 in patients with advanced colorectal cancer, Chong et al. delivered a dose to tumor of 1,200 to 3,300 cGy with a single injection of agent at the maximum tolerated dose.

Although doses of 2,000 Gy are effective in many lymphomas, solid tumors generally require doses in the range of 4,000 to 5,500 cGy. Some characteristics of 131I-huA33 suggest that this agent may provide improved radiation dosing. For example, the A33 antigen is a transmembrane protein that is not rapidly eliminated by lysosomal degradation, allowing longer tumor residence time of the radioconjugate. In addition, 131I is a β-emitter with a relatively long half-life (192 hours) and a particle range of ~2.0 mm, permitting irradiation of several cell layers and penetration to adjacent antigen-negative cells.

The future of radioimmunotherapy for solid tumors depends on the ability to augment the modest radiation dose provided by this modality. Fractionated dose delivery reduces the toxicity of external beam radiation therapy. In contrast, although fractionated delivery of radioimmunotherapy may improve the distribution of agent throughout the tumor, it is unlikely to achieve higher effective tumor doses (6). In support of this, preliminary studies of fractionated radioimmunotherapy using 131I-cG250 in metastatic renal cancer found that fractionation did not reduce hematopoietic toxicity (7). Other options currently under investigation for improving the effective delivery are immunotoxins, cytokines, and gene transduction.

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radiation dose include concurrent delivery of external beam radiation, administration of marrow-ablative radioimmuno-
therapy doses with stem cell transplantation, or combination with radiation-sensitizing chemotherapy.

Advanced colorectal cancer is a common and highly lethal disease, and new systemic therapies are desperately needed to improve treatment outcomes for these patients. Hopefully, lessons learned from the recent success of radioimmunotherapy for treatment of refractory lymphoma can be extended to define a role for this modality in colorectal cancer management. Future studies should focus on combination therapies in populations most likely to achieve clinical benefit.

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