A Pragmatic Perspective on Molecular Targeted Radionuclide Therapy

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This collection of reviews and papers on targeted radionuclide therapy provides a snapshot of the current status of modern clinical applications of therapeutic nuclear medicine. The editors have chosen a pragmatic perspective intended to offer relevant advice to nuclear medicine practitioners and other professionals who may be actively involved in radionuclide therapy to provide them with a summary of suggested patterns of practice for common radionuclide therapies now available. We also include a forecast of the near-term opportunities that are likely to determine practice in the next few years.

CAPTURING THE NEW BIOLOGY FOR PATIENT CARE: THE MOLECULAR NATURE OF TARGETED THERAPY

Targeted therapy is predominantly molecular, in the sense that efficacy is dependent on a therapeutic advantage offered by interaction of the agent with key molecular sites and receptors on the target tissue. Some of the targeting events depend on physicochemical events, such as interaction with the bone-seeking radionuclide and the hydroxyapatite crystal. Others are receptor based, such as the interaction of antibodies and peptides with tissue-specific receptors underlying the targeting process. The approved radiopharmaceuticals themselves offer a range of complexities, beginning with simple ionic forms, such as ^{131}I-sodium iodide and ^{89}Sr-chloride, to antibodies that target the differentiation antigen CD20 on human lymphoma (Table 1).

CURRENT PRACTICE OF TARGETED THERAPY

Thyroid cancer is the only solid tumor that has a U.S. Food and Drug Administration–approved therapy based on targeted radionuclide therapy. ^{131}I-NaI therapy of thyroid cancer has been a mainstay of nuclear medicine and was the first molecular radiotherapy, having been practiced for more than 5 decades (*1*). It is generally accepted that in high-risk patients, thyroid remnant ablation after surgery is an effective procedure that reduces the chances of recurrence, morbidity, and death (*2*). A significant fraction of patients with metastatic thyroid cancer who concentrate ^{131}I well will be cured of their disease. Response is best when the disease is small. Modern practice takes advantage of the availability of recombinant thyroid-stimulating hormone and improved diagnostic approaches, included thyroglobulin assays to detect early disease and monitor treatment (*3*). ^{18}F-FDG PET has proven to be invaluable in staging tumors and planning therapy in patients with advanced disease (*4*). Management of thyroid cancer must be multidisciplinary, involving nuclear medicine specialists, endocrinologists, medical oncologists, surgical oncologists, and radiation oncologists at various stages of this protean disease.

Debilitating pain syndromes are treated effectively with targeted therapies to bone, using several radionuclides, such as ^{153}Sm, ^{89}Sr, and ^{186}Re (*5,6*). It is estimated that metastatic bone disease occurred in about 30,000 prostate cancer and 30,000 breast cancer patients in the United States in 2004. The use of targeted therapy relieves pain effectively in advanced prostate, breast, and lung cancer in about 67% of patients, with an acceptable toxicity that is predominantly hematopoietic. Radionuclide therapy targeted to bone increases the time to development of additional metastatic sites and may be used in combination with chemotherapy to prolong survival (*7*). Treatment also increases quality of life, in part by reducing the need for narcotics to control pain.

Non-Hodgkin's lymphoma is another tumor with increasing incidence, and 55,000 cases were expected in 2004 in the United States. Antibodies, both stable and radioactive, are now a mainstay in therapy of this disease (*8,9*). Two New Drug Applications (NDAs) have been awarded for antibodies that recognize the antigen CD20 on tumor cells: Zevalin (Biogen Idec, Inc.), an antibody product labeled with ^{90}Y, and Bexxar (GlaxoSmithKline/Corixa), an ^{131}I preparation. Both of these antibodies are effective and induce major responses in about 75% of patients, even when the patient has been heavily pretreated with chemotherapy.

THE PATIENT-CENTERED NUCLEAR MEDICINE PRACTICE

Much of nuclear medicine is diagnostic. Because we are consultants to other physicians for this aspect of our prac-

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TABLE 1
Therapeutic Radiopharmaceuticals with Current NDAs in the United States*

Radiopharmaceutical	Brand name	Description	Indication for Therapy	Usual dose range
^{32}P-chromic phosphate	Phospho-coll	Intracavity colloidal injection of β-radiation to treat metastatic effusions	Peritoneal tumor implants Pleural tumor implants Tumor (in ovarian and prostate cancer)	10–20 mC 6–12 mCi .1–.5 mC/g
Ibritumomabtiuxetan (^{111}In/^{90}Y)	Zevalin	Monoclonal antibody specific for normal and malignant (lymphoma) B cells	Localization and treatment of non-Hodgkin's lymphoma	^{111}In 5 mCi ^{90}Y: .3–.4 mCi/kg
^{131}I-tositumomab	Bexxar	Monoclonal antibody specific for normal and malignant (lymphoma) B cells	Localization and treatment of non-Hodgkin's lymphoma	Dosimetric: 5 mCi Therapy: ~50–200 mCi
^{153}Sm-lexidronam	Quadramet	Localizes in bone metastases with β-radiation destroying nerve endings	Relief of pain from bone metastases	1 mCi/kg
^{131}I-sodium iodide	Iodotope	β- (destructive) and γ-radiation localizes in thyroid as it is organized to thyroid hormone	Thyroid function, imaging: Hyperthyroidism oral therapy: Cancer oral therapy:	5–100 uC 4–10 mCi 30–150 mCi
^{32}P-sodium phosphate		Localizes in bone with β-radiation damaging bone marrow production and nerve endings	p. vera: CLL, CML: Bone mets:	3–5 mCi 1–3 mCi 10–21 mC
^{89}Sr-chloride	Metastron	Localizes in bone metastases with β-radiation destroying nerve endings	Relief of pain due to bone metastases:	4 mCi

*List compiled by Mark Soffing, MS, RPh, BCNP, from available sources, including package inserts; personal communication, 2004.

tice, patient contact may be minimal. On the other hand, therapeutic nuclear medicine involves us deeply in the day-to-day care of the patient, because we cannot avoid intense patient contact during the time when the patient is under active treatment. Some of our patients, such as those who require retreatment with radioactivity and follow-up over the course of several years, may come to regard us as their primary physicians. For some of us, this is highly rewarding. In this capacity we are required to make key decisions about many aspects of management, including diagnosing and treating important complications or coordinating therapy by other specialists, such as radiation oncologists and medical oncologists. Clearly, as therapy increases in importance within nuclear medicine, our training programs are going to have to meet a higher standard in preparing the nuclear physician for a larger role in patient management.

THE PATIENT'S PERSPECTIVE

Patient support groups are emerging with vested interests in improving targeted therapy. In part, this is a matter of demographics and the growing demand for nuclear medicine consultation, particularly for thyroid cancer and neuroendocrine tumors.

According to Surveillance, Epidemiology, and End Results Program data, thyroid cancer is the most rapidly growing in cancer incidence and was predicted to reach 23,000 cases in the United States during 2004 (*10*). The cover of this supplement reflects the fact that thyroid cancer in young women has the most rapidly increasing incidence of any cancer. The picture of this young woman was produced by a patient support group, the Light of Life (LOL) Foundation. The goal of LOL is to provide patients with answers to common questions about thyroid cancer and care, including the appropriate use of radioactive iodine and complications that may occur. There were approximately 9,000 carcinoid cancers in the United States in 2004, and carcinoid patient groups are also active, providing information about this disease and organizing frequent meetings with professional speakers.

For a growing number of patients, including those with thyroid cancer, lymphoma, metastatic bone involvement with prostate and breast cancer, and carcinoid tumors (especially in Europe), radionuclide therapy has already become an important component of modern medical practice. In the near future, as peptide therapy of endocrine tumors achieves regulatory approval in the United States and becomes widespread, we can anticipate and must welcome the emerging role of interested patients and their families as partners in care in radionuclide therapy.

A BRIGHT FUTURE FOR TARGETED THERAPY

NDAs are on the near horizon for targeted peptides, and this promising form of therapy is likely to be very important for treating well-differentiated endocrine tumors of the gastrointestinal tract and thyroid cancer without radioiodine accumulation. Additional antibody preparations, in particular for lymphoma, are also being studied on the basis of improved methods of targeting, including multistep techniques. In this supplement, Krenning and Goldenberg, pioneers in targeted therapy, offer their perspective on these short-term prospects and also identify important problems that must be overcome if we are to achieve optimal use for peptides and antibodies for

targeted radiotherapy across the entire spectrum of tumor types. Both of these authorities recognize a growing role for image guidance, especially with PET, for monitoring dosimetry and optimizing targeting.

Mapping the human genome is the greatest scientific achievement of this century. The molecular biology methodologies that were developed during the human genome project have by themselves led directly to the discovery of improved molecular targets for targeted therapy. As such, it is likely that the revolution in knowledge about biology will affect targeted radiotherapy as well. Also, we are already beginning to see a trend toward increasing sophistication of radiopharmaceutical formulations, including antibodies, minibodies, fusion proteins, peptides, and small organic molecules. This will inevitably lead to better agents and better patterns of practice for established therapeutics.

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