New Research Developments Increase Therapeutic Options for Thyroid Cancer and Bone Pain Palliation

Ongoing efforts to improve long-term standard therapies for thyroid diseases and metastatic bone pain relief offer clinicians a wider array of options for providing optimum patient care.

Two nuclear medicine mainstays—radioiodine therapy and bone pain palliation—are seeing promising innovations that may increase the number of approaches available in patient care. Encouraging results demonstrated by recombinant human thyroid-stimulating hormone (TSH) in recent clinical trials and the emergence of several new radiopharmaceuticals for bone pain palliation (with two approved recently by the FDA) offer clinicians a wider range of diagnostic and therapeutic choices. That range continues to expand as research reveals additional applications for the new commercially approved agents as well as those still awaiting FDA approval.

Recombinant Human TSH

Approximately 188,000 Americans (mostly women) have had thyroid cancer, and about 13,000 new cases of thyroid cancer are diagnosed in the U.S. each year. Radioiodine therapy remains the most commonly used treatment for this cancer and for hyperthyroidism. "For very few cancers do we have a material which is so specific and so lethal to cancer cells," says Edward B. Silberstein, MD, professor of internal medicine and radiology at the University of Cincinnati Medical Center. One limitation to radioiodine therapy, however, is symptomatic hypothyroidism, which patients may experience when they discontinue taking synthetic thyroid hormone supplements for 3 to 6 weeks during therapy to ensure sufficient levels of TSH for adequate radioiodine uptake. These symptoms, which include fatigue, weight gain, constipation, mental dullness, lethargy and depression, are particularly debilitating over the latter part of the withdrawal period and may interfere with a patient's ability to perform his or her daily activities.

Genzyme Corp. (Cambridge, MA) has developed an injectable recombinant human TSH (Thyrogen®) that automatically elevates TSH levels and allows patients to remain on their hormone replacement therapy, thereby eliminating the physical discomforts of hypothyroidism. Recombinant human TSH is a highly purified form of the naturally occurring human protein TSH. Because its DNA sequence is identical to that encoded by the human genome, it is unlikely to induce an immunological response in humans such as that observed from bovine and porcine TSH extracts.

A recombinant human TSH that eliminates the hypothyroidism patients experience during radioiodine treatment could improve long-term treatment and management of this disease. "In some compassionate trials in patients with advanced thyroid cancer, we've found it to have a very significant potency for rapidly stimulating uptake of radioactive iodine so that these patients can avoid a prolonged period of hypothyroidism," says Steven M. Larson, MD, chief of nuclear medicine service at Memorial Sloan-Kettering Cancer Center. "I think that this product will have great impact in the future for treating patients with disseminated thyroid cancer because you won't have to stop thyroid hormone treatment, you won't have to put the patient both at the risk and inconvenience of being so hypothyroid and you'll still be able to treat the patient with a very effective radionuclide, ^{131}I, for thyroid cancer."

Genzyme recently completed confirmatory Phase III trials for recombinant human TSH. Investigators from 11 U.S. and 3 European medical centers participated in the study of 220 patients divided into two dosing groups. The first group (113 patients) received a daily injection of 0.9 mg recombinant human TSH for 2 days, and the second group (107 patients) received an injection of 0.9 mg every 72 hours over a 7-day period. The radioiodine scans of 92% to 93% of patients given recombinant human TSH were equivalent or superior to the scans of patients whose thyroid hormone supplements had been withdrawn. Researchers found no statistical difference between the two dosing regimens. No patient in the trial had an immunological response to the recombinant human TSH. These data confirm and demonstrate improvement on the results of a 1994 Phase III trial that showed that recombinant human TSH produced scans equivalent or superior to withdrawal scans in 86% of patients.

Genzyme's future plans include filing a new drug application with the FDA as well as submitting applications for regulatory approval in Europe (later this year) and Canada (early 1998).

Bone Pain Palliation

Although researchers have spent decades investigating the efficacy of both ^{32}P and ^{89}Sr for use in metastatic bone pain palliation, research and development in this area intensified in the early 1980s, resulting in the commercial availability of both ^{89}Sr and ^{153}Sm. However, researchers are still investigat-

ing other standard palliative agents, such as ^{32}P, in comparative studies.

Phosphorus-32 The International Atomic Energy Agency (IAEA) is conducting an ongoing study, designed by its nuclear medicine division, that compares the use of oral ^{32}P to intravenous ^{89}Sr in developing countries that generally cannot afford the more expensive beta emitters. "The costs for intravenous materials such as ^{89}Sr and ^{153}Sm run $2250, according to the *Medical Letter*, August 29, 1997," explains Silberstein. "Oral phosphorus is cheaper because you don't have to make it sterile or pyrogen-free. If it has efficacy and safety equal to intravenous strontium, then you've got a real winner." Test sites for the study are located in Bombay and New Delhi, India; Ljubljana, Slovenia; Bandung, Indonesia; and South America.

Although little preliminary data are available, the goal of the study is to correlate measurements of pain perception as well as information on medication use, quality of sleep and changes in daily activities. There are some concerns, however, because the diets in many developing countries differ from those in more developed nations where phosphate absorption may be greater, or less, than that in the experimental sites. The IAEA hopes to complete and publish the results of the study in 1998.

Strontium-89 (Metastron®) Researchers are studying two new applications for ^{89}Sr, which has proven to be highly effective for relieving bone pain. "Our major focus is exploring its usefulness for treating hormone-resistant prostate cancer by combining it with standard chemotherapies such as estramustine and vinblastine and seeing if there is an additive or synergistic effect," says Nicholas Borys, MD, director of medical affairs at Amersham Healthcare, Arlington Heights, IL. The idea evolved from findings in the pivotal Trans-Canada study, which was followed by work done at M.D. Anderson combining ^{89}Sr with doxorubicin (Adriamycin®). Researchers achieved response rates of 30% to 35% and found that there was an additive effect when the two therapies were combined. The early results of the current Phase II study endpoints, such as prostate-specific antigen and time to treatment failure, look promising and were presented at the recent American Society of Clinical Oncology meeting in Denver.

Other studies under way at the University of California at San Diego and Brown University may elucidate the biocellular mechanisms of ^{89}Sr. "We're beginning to find data that there might be a marker in the blood indicating who is going to respond to Metastron and who isn't going to respond," says Borys. Amersham hopes to release some preliminary data from this study in the next few months.

Samarium-153 EDTMP (Quadramet®) Samarium-153 EDTMP was approved by the FDA in late March 1997 and is the newest commercially available bone pain palliation agent. Two important advantages of this radiopharmaceutical are its short half-life, which allows for more rapid onset of pain relief and more frequent repeat dosing, and its rapid excretion from the body, which might allow greater success with peripheral blood stem cell support of pancytopenia.

The results of a randomized, dose-controlled Phase II study for ^{153}Sm-EDTMP were recently published in the *European Journal of Cancer* (1997;33:1583-1591). In that study, ^{153}Sm-EDTMP was administered to 114 patients with painful bone metastases: 55 received a single dose of 0.5 mCi/kg, and 59 received a single dose of 1.0 mCi/kg. Patients evaluated efficacy daily during the first 4 weeks. Patient-related efficacy assessments included degree of pain, level of daytime discomfort, quality of sleep and pain relief. By Week 4, 59% of the patients in the 0.5-mCi/kg group and 70% of the patients in the 1.0-mCi/kg group experienced some degree of pain relief. Among subsets of patients, female patients with breast cancer receiving 1.0 mCi/kg had the most noticeable improvement. Long-term follow-up also revealed longer survival rates among breast cancer patients who received the higher dose.

CYTOGEN Corporation (Princeton, NJ), which developed ^{153}Sm-EDTMP, is also investigating other applications. According to William Goeckeler, PhD, of CYTOGEN's clinical investigations department, new studies will explore combining ^{153}Sm-EDTMP with approved therapies such as external radiation therapy, chemotherapy and possibly bisphosphonate therapy. Phase II dose escalation studies are currently under way to determine what effect, if any, ^{153}Sm-EDTMP has during the clinical course in treating tumors with a high propensity to metastasize to the bone. "This would typically be men with prostate cancer [which] has metastasized but at an earlier stage of the disease than we've [studied] so far. Normally at this point, they'd get treated with hormonal therapy," says Goeckeler. "Right now we're escalating the doses to see what sort of toxicities we get when we administer it repetitively and at higher doses. Our intent down the road will be to see if combining Quadramet with hormonal therapy in these patients could impact the course of their disease."

In other research, the Mayo Clinic has initiated an independent study to see if the agent can be used to treat primary bone tumors. "We have reason to believe, based on animal studies, that the compound has activity in terms of therapy in primary bone tumors," says Goeckeler. CYTOGEN, which is supplying ^{153}Sm-EDTMP for the study, will be organizing its own primary bone tumor study in the near future. CYTOGEN has also initiated a Phase I dose escalation study to determine the efficacy of ^{153}Sm-EDTMP in the treatment of painful bone metastases in children with cancer.

Tin-117m Stannic-DPTA Tin-117m has properties similar to other radiopharmaceuticals used for bone pain palliation except for one fundamental difference: it is not a beta emitter. Therefore, hematological toxicity is not a limitation to its use. "Tin-117m emits conversion electrons in its spectrum," says Suresh Srivastava, PhD, head of the radionuclide and radiopharmaceutical division, medical department, Brookhaven National Laboratory (BNL), and discoverer of the agent. According to Srivastava, the range in the tissue of ^{117m}Sn's two main conversion electrons is fixed at 0.22 mm and 0.29 mm, respectively. This shorter range should preferentially deposit the radiation dose onto the target, in this case the bone tumor, with-

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Evaluation Center, Chicago
- Duke University, Durham, NC
- ECRI, Plymouth Meeting, PA
- Johns Hopkins University, Baltimore
- McMaster University, Hamilton, Ontario
- MetaWorks, Inc., Boston
- New England Medical Center, Boston
- Oregon Health Sciences University, Portland
- RAND Corporation, Santa Monica, CA
- Research Triangle Institute and University of North Carolina at Chapel Hill
- University of California, San Francisco, and Stanford University
- University of Texas, San Antonio

The reports produced by the EPCs will have a significant impact on the quality of health care services by providing much-needed critical evaluations of the available scientific literature regarding clinical interventions and technologies, said John M. Eisenberg, MD, AHCPR administrator. This will be invaluable not only to individual clinicians, health plans, providers and purchasers, but also to the health care system as a whole by providing important information to help reduce unnecessary variations in medical practice.

EANM Partners with SNM on Utilization Database

During the European Association of Nuclear Medicine (EANM) meeting in September, a partnership was formed with the Society of Nuclear Medicine (SNM) to undertake a joint program aimed primarily at the analysis of nuclear medicine practice. SNM president H. William Strauss, MD, and EANM president Angelika Delaloye, MD, signed the agreement in Glasgow.

The goal is to develop an aggregate utilization analysis database to collect information on nuclear medicine procedures, equipment and personnel, as well as on institution demographics.

The Commission on Health Care Policy and Practice has contacted a European representative about informing European physicians of CPT codes for the most frequently performed procedures in the U.S. (based on 1996 Medicare data) so that they may collect data in a similar format. This will allow the data to be analyzed in an international context.

EANM will conduct a pilot of three European cities (Paris, London and a third city yet to be determined) over the next several months to analyze the differences in practices by country and to draw appropriate conclusions to further develop and extend the project throughout Europe.

As in the U.S. project, the Europeans will ensure anonymity and confidentiality of data, update the database at least twice a year and distribute reports to institutions that participate in the project. SNM leaders reported enthusiasm for this collaborative project, which, they hope, will provide important data for reimbursement and managed care issues.

—Wendy J.M. Smith, MPH, is the SNM director of health care policy.

Research Developments for Thyroid Cancer

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out penetrating too much to cause excessive radiation to the bone marrow.

BNL and Diatide, Inc. (Londonderry, NH), which is licensed to manufacture and market the agent, will initiate an extended Phase II/III clinical trial with more than 200 patients. They are hoping that the data from the Phase II/III study will corroborate preliminary results from an earlier Phase I/II trial in 47 patients. In the earlier study, 30 of 40 patients (75%) experienced complete (n = 12) or significant (n = 18) pain relief during an observation period of 1 to 4 months. Of the 40 assessable patients, 2 patients experienced Grade 2 and 1 patient experienced Grade 3 white blood cell toxicity. No patients demonstrated clinically significant platelet toxicity. (These values are lower than those reported for other agents.)

Because of its potentially low hematological toxicity, researchers believe that ^{117m}Sn could be useful for treatment of primary bone tumors and rheumatoid arthritis. BNL is planning an experimental trial using ^{117m}Sn in dogs with primary osteoblastic osteosarcoma and a preliminary biodistribution study in patients with rheumatoid arthritis. In addition, studies are in development that would investigate the additive effect ^{117m}Sn might have when combined with external beam therapy as well as with several other chemotherapies.

—Jeffrey E. Williams