Radiopharmaceuticals as therapeutic agents in medical care and treatment

A new IAEA research programme assists countries interested in the use of improved radiopharmaceuticals for medical therapy

by Hernan Vera-Ruiz

Radiation applications in medical research, care, and treatment today are being used to help millions of patients throughout the world.

Perhaps most widely known are diagnostic applications in the field of nuclear medicine, which has seen significant expansion over the past two decades. Such applications typically employ radionuclides as tracers to aid in diagnosing or studying medical conditions. Iodine-131, for example, is effective in locating brain tumours, and in determining liver and thyroid activity, and technetium-99m is a common agent for imaging studies.

Other radiation applications are directed at treatment of serious disease, typically cancers. These include the well-known use of cobalt-60 in cancer therapy, for example. Traditionally, other radionuclides, including iodine-131, phosphorus-32, and strontium-89, were used in the fields of oncology, endocrinology, and rheumatology. The incorporation of more radionuclides into the armamentarium of medical therapy during the last 30-40 years, however, has been slow for a variety of reasons.

In recent years, however, the medical community has seen a renaissance of therapeutic radiation applications, particularly of strontium-89 for metastatic bone pain. The change has come about largely through advances over the past decade in the radiopharmaceutical industry, the greater availability of radionuclides with improved nuclear and chemical characteristics for medical uses, and encouraging results from clinical studies on uses of radiopharmaceuticals for therapy.

Radiopharmaceuticals used as therapeutic agents (frequently known as RPTs) are designed to deliver high doses of radiation to selected malignant sites in target organs or tissues, while minimizing the radiation doses to surrounding healthy cells. Over the past several years, several types of RPTs with special properties, including compounds for labelling monoclonal antibodies, have been used in animal and human clinical trials with promising results.

The modern trend in radiopharmaceutical research for oncology is the development of RPTs that may be said to be tumour-seeking and tumour-specific. In therapeutic radiopharmaceutical applications—unlike the case of external radiation therapy where the radiation from an external sealed radioactive source is focused on the site to be irradiated—the product is administered to the patient orally or intravenously and is selectively taken up or localized in the site to be irradiated. Suitable agents have to be designed to exploit the metabolic and biological characteristics of tumours, so as to guide the RPT and ensure proper localized treatment.

Among the promising RPTs being reported in the medical literature are rhenium-186 and samarium-153. Both can be produced in research reactors available in many countries.

In light of growing medical interest in the use of RPTs, and to foster continuing research in this field, the IAEA initiated a co-ordinated research programme in early 1993. This programme complements ongoing IAEA activities, largely through its technical co-operation programme, designed to assist countries in developing indigenous capabilities and expertise in the production of radionuclides for medical and industrial uses.

The research programme's objectives are to optimize the production of therapeutic radiopharmaceuticals in research reactors, particularly taking into account the characteristics of reactors operating in developing countries. It also will seek to further develop protocols for radiolabelling and quality control. Countries from Africa, Asia and the Pacific, and Latin America are participating in the work. Separately, the IAEA also is implementing a co-ordinated re-

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search programme on therapeutic applications of radionuclides in patients with malignant metastases in bones.

This article presents a brief selective overview of some of the latest developments in the production and preparation of RPTs, specifically those being evaluated for the palliation of pain in bone cancers.

Selection of suitable radionuclides

For therapeutic purposes, the selection of a suitable radionuclide for a specific application takes into account a number of factors. These include the physical characteristics of the radionuclide itself, mainly the type and energy of the radiation emitted and the radionuclide's half life, and the exact location of the target area to be treated.

The rationale or strategy in RPT is to deposit the greatest amount of energy in the shortest time to the malignant target cells, while sparing the healthy ones from unwanted radiation. The deposition of energy is measured by what is known as Linear Energy Transfer (LET), which is different for alpha, beta, or gamma radiation.

Gamma radiation exhibits low values of LET, as it penetrates relatively deeply, on the order of several centimeters, and does not deposit much energy along its track. Consequently, pure gamma-emitting radionuclides usually are not used for therapeutic purposes. Particle-emitting radionuclides, on the other hand, deposit greater energy near the site of localization, and hence are more suitable for therapeutic applications.

In practice, radionuclides that emit beta particles, as well as those capturing electrons and emitting what are known as Auger electrons, are the only ones that have been used in therapeutic nuclear medicine. This is due to various reasons. Beta particles have penetration ranges in tissue on the order of millimeters to a few centimeters, appropriate depths for the irradiation of small- to medium-sized tumours. Secondly, some of the most promising beta-emitting radionuclides have desirable half-lives, varying from several hours to days. Lastly, many of these radionuclides are easily produced in nuclear research reactors, facilitating their availability. *(See table.)*

Radionuclides emitting beta particles are widely used. They include phosphorus-32, strontium-89, and iodine-131, which might be considered the "first generation" of therapeutic radionuclides. Their use in medicine dates back to the late 1930s. It is estimated, for example, that more than one million patients around the world have been safely and effectively treated with iodine-131 for hyperthyroidism. Currently, a labelled compound known as iodine-131 MIBG is being used to treat a variety of tumours.

Among the "second generation" of beta-emitting RPTs are samarium-153, rhenium-186, copper-67, and holmium-166.

Among alpha-particle emitters, only two radionuclides have been considered and studied as potential therapeutic agents: astatine-211 and bismuth-212. Largely because of the extremely high radiotoxicity and short half-lives of alpha-emitting RPTs, a good deal of laboratory research still is needed to develop them for medical therapy uses.

Radionuclides for medical therapy

Beta emitters:

Radionuclide	Half-life	Maximum energy (megavolts)
Phosphorus-32	14.3 days	1.71
Strontium-89	50.5 days	1.46
Yttrium-90	2.7 days	2.27
Iodine-131	8.0 days	0.606
Dysprosium-165	2.3 hours	1.34
Samarium-153	1.95 days	0.80
Holmium-166	1.1 day	1.6
Rhenium-186	89.3 hours	1.07
Rhenium-188	17.0 hours	2.11
Copper-67	2.4 days	0.57

Auger emitters:

Radionuclide	Half-life
Iodine-123	13.3 hours
Iodine-125	59.7 days
Mercury-197	2.7 days
Gallium-67	3.2 days
Platinum-193m	4.3 days
Ruthenium-97	2.9 days

Alpha emitters:

Radionuclide	Half-life	Mean energy (MeV)
Bismuth-212	60.5 minutes	7.8
Astatine-211	7.2 hours	6.7
Fermium-225	20.1 hours	7.0

Production of radionuclides

Independent of intended use, radionuclides can be produced in nuclear research reactors and in particle accelerators such as cyclotrons. Of the more than 300 nuclear research reactors in operation throughout the world, more than 80 are installed in developing countries. Cyclotrons designed for radionuclide production are being

Radionuclides produced in research reactors for potential bone cancer therapy

Radionuclide	Half-life	Maximum energy (MeV)
Rhenium-186	89.3 hours	1.07
Samarium-153	46.8 hours	0.80
Holmium-166	26.4 hours	1.60
Lutetium-177	6.7 days	0.50
Dysprosium-165	2.3 hours	1.34
Yttrium-90	64.8 hours	2.27
Strontium-89	50.5 days	1.46

installed in increasing numbers in both industrialized and developing countries. It is estimated that some 150 cyclotrons totally or partially dedicated to radionuclide production will be in operation in the next few years.

Nuclear research reactors. As prolific sources of low energy neutrons, nuclear reactors are used to produce radionuclides via neutron activation of appropriate target materials.

Depending upon the neutron flux of the nuclear reactor, radionuclides produced by the neutron activation method are in general of low to medium specific radioactivity. This fact severely limits the production of certain radionuclides, such as those required in the promising field of radioimmunotheraphy using labelled monoclonal antibodies. The problem could be solved in part, albeit at higher cost, by using isotopically enriched target materials. Using research reactors having a high neutron flux also would increase the specific radioactivity of radionuclides, but there are not many such research reactors around the world.

A number of important medical applications, however, do not require high specific activities. This is the case for therapeutic bone agents based on bone-seeking radiopharmaceuticals, for example. These radionuclides can be produced without major difficulties in nuclear research reactors already installed in developing countries. *(See table.)*

Cyclotrons. The most common charged-particle accelerator used for the production of radionuclides is the cyclotron. These machines accelerate light particles at high energies that upon striking suitable targets can induce nuclear reactions producing radionuclides with extremely high specific activity. Cyclotrons can produce a wider spectrum of radionuclides than nuclear reactors, and they are especially suited for producing radionuclides for the labelling of monoclonal antibodies. Copper-67, for instance, can be produced by bombarding a zinc target with energetic proton particles. For the time being however, cyclotrons are less widely available than research reactors, particularly in developing countries.

Radiopharmaceuticals for cancer therapy

Over the past number of years, considerable interest has emerged in the use of radiopharmaceuticals to relieve intense bone pain resulting from metastasis from breast, prostate, and lung cancer. Their application has been demonstrated in clinical practice, and a number of governmental and commercial laboratories are actively engaged in the development and clinical evaluation of RPTs for the treatment of patients with painful skeletal metastasis.

The prevalence of metastatic bone cancer in nearly all countries creates a large need for the development of new palliative agents. It is estimated that about half of all patients with carcinomas of the prostate, breast, and lung eventually develop skeletal metastasis.

The disease causes intense pain and suffering for patients. The pain is frequently relieved by the use of analgesics or even narcotics such as morphine when the pain is intolerable. For terminal patients, the use of bone-seeking RPT may be a desirable alternative to narcotics.

The most appropriate radionuclides for bone therapy are those decaying by the emission of medium energy beta particles. Beta particles of energy between 1 to 2 MeV have been shown to be effective since they are able to penetrate only the required few millimeters of the malignant tissue without compromising the bone marrow too much, a consideration of paramount importance when designing new RPT for bone therapy.

Besides phosphorus-32 and strontium-89, a number of radionuclides are rapidly drawing interest for bone cancer therapy. These include samarium-153, rhenium-186, and to a lesser extent holmium-166 and dysprosium-165.

Rhenium-186, samarium-153, and a number of other bone-seeking radionuclides can be produced in research reactors of medium and high neutron flux by neutron irradiation of appropriated targets. Although their availability is limited within the developing world, research reactors having a high neutron flux are operating in Indonesia, Peru, China, and India, for example.

Over the past few years, a number of bone-seeking compounds of rhenium and samarium have been investigated for the relief of bone pain. Some of these compounds now are undergoing clinical trials in the United States, Europe, China, Japan, and Australia. The studies show that these compounds of rhenium and samarium are effective in alleviating the pain in disseminated bone metastasis at injected doses in the range of 0.2 to 1.0 milli-curies per kilogram of body weight.

It is observed that this amount of radioactivity delivers radiation doses sufficient for pain relief with minimal to mild suppression of bone marrow. Myelotoxicity studies indicate only a transient depression of platelet, granulocyte, and lymphocytes counts.

Most of the reported studies indicate significant pain relief in 60% to 80 % of the patients over a time period of four to 35 weeks. Complete pain relief is observed in 20% of the cases. Other than transient bone marrow suppression over two to three weeks, no other significant toxic side effects are reported. Further studies are needed to confirm these results in a variety of oncological situations, which in turn will allow the formulation of appropriate clinical protocols.

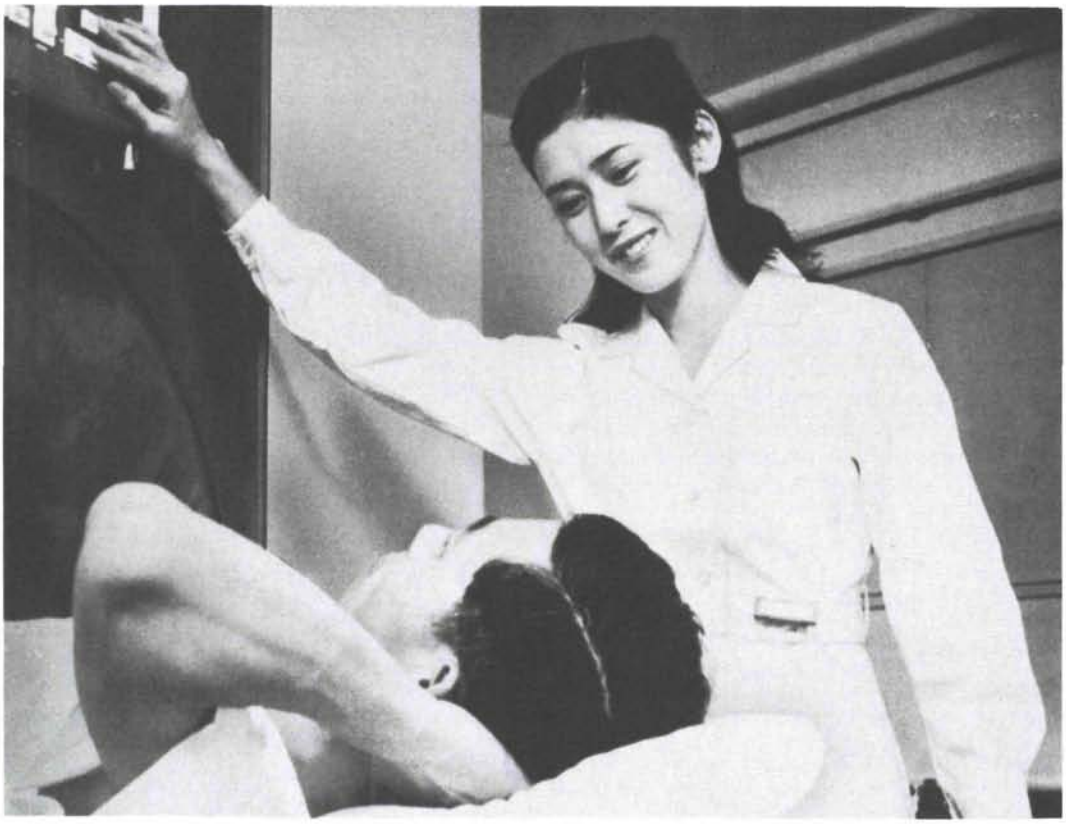
Studies in dogs with primary and metastatic bone cancer showed that in about 20% of the cases this form of therapy can have curative effects as well, with a complete remission of the disease. A follow-up study of humans suggested similar conclusions. If these findings are confirmed, therapeutic nuclear medicine will expand and effectively complement other therapy modalities.

Possibilities in developing countries

Many nuclear research reactors operating in developing countries are suitable for the production of therapeutic radiopharmaceuticals. Moreover, a good level of expertise exists in the production of radionuclides and radiopharmaceuticals, and basic laboratory facilities have been established. Consequently, it appears that developing countries have excellent possibilities to attempt an indigenous production of the radionuclides rhenium and samarium and their labelled compounds for therapeutic nuclear medicine, particularly those compounds used for the palliation of pain from metastatic bone cancer.

Potential drawbacks are the availability of enriched target materials at affordable prices, and investigation would be needed to demonstrate the feasibility of using more inexpensive and abundant natural target materials. In some countries, the low power levels of their research reactors would be a disadvantage, though not an insurmountable one.

It is in response to this range of opportunities and potential beneficial medical applications that the IAEA has launched its new co-ordinated research programmes on the production and application of therapeutic radiopharmaceuticals. Through this co-operative approach, interested countries will be able to strengthen their capabilities in nuclear medicine for effective health care and treatment. ❐



A number of radiopharmaceuticals frequently are used for diagnostic imaging studies. Others are being studied for use in medical therapy of cancers. (Credit: Tech-Ops)