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EDITORIAL

Therapy with radionuclides
clinical acceptance is overdue

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العلاج بالنُويدات المشعة
تـأخر وقت القبول السريري

لامك اللامكي

In this issue, Drs. Bererhi and Constable[1] have published an important paper on the radiation doses received by relatives of patients after radioiodine therapy for thyroid cancer or for hyperthyroid Graves' disease. Basically, they have shown that the radiation doses to the relatives are too small to be an important consideration in radioiodine therapy. The authors are, thus, suggesting much less restrictive precautions, and justifiably so. They have rightly pointed out that in other countries—at least in the United States and in Britain—the regulations are much less demanding as a result of similar earlier studies done in those countries. The U.S. Nuclear Regulatory Commission (NRC) no longer dictates the exact load of radioactive drug within the patient as the limiting factor prior to being discharged from the hospital. Instead, the exposure to the relatives and members of the public is the limiting factor. A patient may be released as long as 'the effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (0.5 rem).[2] It is up to the treating physician to decide whether the risk of exposure to other people is low enough, (under 0.5 rem) before releasing the treated individual from his/her control.[2] In fact, in the United States, it is now possible to treat patients with thyroid cancer using 3700–7400 MBq (100–200 mCi) of radioiodine-131 (^{131}I) without admission to hospital. Dr. Bererhi's article[1] will go a long way towards alleviating the anxieties of the public and physicians in Oman and elsewhere.

The perception of the public and the treating physicians regarding radionuclide therapy is particularly important now that there is evidence that radionuclide therapy can contribute significantly in the management of several clinical conditions, both curative and palliative.[3,4] Acceptance of radionuclide therapy by physicians and the public is extremely important, particularly in certain regions where specific kinds of malignancies are common. For example, if breast cancer is relatively common in Oman, then palliative radionuclide therapy is most relevant to patients with painful metastasis to the bones. Likewise, radionuclide therapy can help painful bone metastases of other cancers, such as prostate cancer.

Therapy for bone pain using strontium-89 (^{89}Sr) is probably one of the best examples of the palliative role of radionuclides in oncology, while therapy with ^{131}I as used by Drs. Bererhi and Constable at SQU is an example of the curative role. Unfortunately, despite the literature support for the use of radionuclide therapy as an effective form of palliation in bone pain of malignancy, from the 1980's,[5] these agents remain under-utilized because of poor understanding of their appropriateness.[6,7] A recent survey among 100 medical oncologists revealed that they perceived the appropriateness of systemic radionuclide therapy for bone pain as 'low'.[6] They were managing their patients primarily with narcotic opioids. There is now evidence in the literature that early utilization of radionuclides is very effective for bone pain in cancer with or without concomitant use of local external radiotherapy, using systemic injections of either ^{89}Sr or samarium-153 (^{153}Sm).[6,8] There is also evidence that radionuclide therapy is cost-effective and this reduction of cost is accompanied by effective pain diminution as measured by McGill Pain Questionnaire Evaluated Survey. There is very little excuse at this stage for allowing patients with metastatic cancer to continue suffering from bone pain.[8–12]

Strontium-89 chloride ($^{89}SrCl_2$) and samarium-153 ethylenediamine tetramethylene phosphoric acid (^{153}Sm-EDTMP) are now both approved by the FDA in the USA and are available in the American market for bone pain. Significant relief from pain is 60%–80%.[3, 11,12] In fact, patients receiving ^{89}Sr had significantly less likelihood of developing a new site of pain compared to external radiation therapy. Other radiolabelled drugs available in other countries for bone pain from metastases

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include rhenium-186 hydroxyethylene diphosphonate (^{186}Re-HEDP) and stannum-117m diethylene triaminpantolositic acid.[13–15] All these have been shown also effective for palliation of bone pain in metastatic disease. Metabolically, strontium is handled in the body much like calcium and is taken up by the bones, thus, reaching the metastatic disease. In the case of ^{186}Re-HEDP, the HEDP moiety is taken up by the bones like other phosphates, thus enabling ^{186}Re to reach the metastatic disease. Likewise, ^{153}Sm is delivered to the bone metastases, because of its phosphate moiety EDTMP.

Most radioisotopes used for bone pain radiate beta (β) particles, which are electrons with maximum energy of between 0.01 MeV and 1.4 MeV. Thus, penetration into tissues is very low, ranging from 2.7 to 5.7 mm. This perhaps explains the relatively low incidence of thrombocytopenia and its transient nature as well as the low incidence of other complications. $^{89}SrCl_2$ and ^{186}Rh-HEDP both cause transient thrombocytopenia.[16,17] Beta-emitting yttrium-90 (^{90}Y) has a β-maximum energy of greater than 2.2 MeV and can, therefore, penetrate tissues up to 11 mm. Phosphorous-32 (^{32}P) has β-maximum energy of 1.7 MeV and a penetrating range of 8.7mm. While most of the radionuclides used for various therapies are in fact beta emitters, a few others emit 'auger electrons' and alpha particles, while fewer still emit non-particulate gamma rays and X-rays during their decay. Gamma rays and X-rays, being photons, can travel longer distances than β or α particles. On the other hand, β and α particles, with their lower penetration ability, deposit all their energy at the site of interest confined within the patient, which gives them a therapeutic advantage over X-rays and gamma rays. This is fortunate for radiation safety[18–20] as there is significant radiation to the patients treated, with little danger of exposure to public contacts. Concern with radiation safety is therefore, related to the handling of excreta and body fluids when we deal only with β emitters, such as ^{89}Sr or ^{186}Re. However, if we use isotopes that emit gamma rays, such as ^{131}I or Bremstrahlung X-rays radiation, then we have to consider the number of hours a treated patient spends in close proximity to relatives and others. There is a lot of interest now in the potential use of α-emitters such as Bismuth-212 (^{212}Bi), Lead-212 (^{212}Pb) and Polonium-212 (^{212}Po). These radionuclides are theoretically more lethal to the cancer cells.[20–22] There is also a high interest in the use of the α emitter Astatine-211 (^{211}At) because it is closely related to iodine in the periodic table, giving us some advantage in labelling technique in view of the experience we have with iodine.

Both α and β emitting radionuclides can be used locally, intra-lesionally[22] or systemically.[23,24] There are several new choices of both α and β emitters now available to the oncologists for radionuclide therapy.[3,4,18] Most of these have to be given systemically, either intravenously or orally, but some are administered locally into the lesion or intracavitary. The other consideration is the chemical form of the radionuclide. Most radionuclides can be used therapeutically just as a salt of an isotope, e.g., $^{89}SrCl_2$, $Na^{131}I$ or ^{32}P chromate. But often they are used to radiolabel physiological tracers, such as ligands, peptides and antibodies and these will be discussed shortly. Whatever form the radionuclides are given, or by whatever route, systemic or local, radionuclide therapy does seem to be effective not only in palliation of pain but also in arresting the growth of some metastasis from several cancers, and even cure some of them.[25]

Radionuclides are gaining increasing importance in the definitive therapy of cancer. For example, ^{153}Sm EDTMP has been used for more definitive therapy of osteosarcomas, rather than just for bone pain. While this is still preliminary, it is a promising supplementary therapy to conventional external radiotherapy of osteosarcomas.[26] Another historic radionuclide therapy which is being used for definitive therapy to either halt or control the disease, rather than just palliation for bone pain is ^{131}I labelled MIBG.[27–29] This was one of the early radiopharmaceuticals used specifically for definitive treatment of metastatic disease. It is effective not only against metastatic pheochromocytoma, but also against many other neuro-endocrine tumours (NET). There are several other radiolabelled physiological tracers, which are used for definitive therapy of metastatic disease. The latest addition to the armamentarium of radionuclides for definitive therapy are the radiolabelled monoclonal antibodies to specific tumour antigens[30–33] and radiolabelled peptides, e.g., somatostatin analogs for tumours that have Somatostatin receptors, as in neuro-endocrine tumours.[34–36]

Radiolabelled antibodies are very promising, especially in the therapy of lymphoma where radioimmuno therapy has been most successful in lymphoma therapy to date.[30–31, 37–41]

There are several studies that showed that radiolabelled monoclonal antibodies against CD-20 and CD-22 antigens of lymphocytes are promising for lymphoma therapy. At our institution we have shown the potential utility of these antibodies; in fact, the potential of radioimmunotherapy for cancer has been recognized in the last decade[20,33,42] and is gradually gaining acceptance.[43–47] The monoclonal antibody goes to the target antigen and carries with it the lethal radionuclides. The exact site of action is variable e.g. there is debate as to whether internalisation of the radiolabelled antibody is necessary before destruction of the tumour cells. It seems, however, that there is now enough evidence to indicate that internalisation is not absolutely necessary for destruction of tumour cells. But the dose to the cell nucleus in micrometastasis using ^{131}I labelled antibodies does depend on the exact sub-cellular position of the ^{131}I.[48] Targeting

the nucleus instead of the cellular membrane could increase the dose to the nucleus ten-fold.[48] Several workers have tried to improve the localization and effectiveness of the radiolabelled antibodies. To this end, pre-targeting is one manoeuvre used in radioimmunotherapy both regional and systemic. Riva[25] describes brain tumours radioimmunotherapy with increased efficiency by pre-targeting with biotin and avidin. Pre-targeting has specific advantages, which are beyond the discussion in this editorial. There are several other manipulations of administration of radiolabelled antibodies that some workers have used to improve the localization and effectiveness of radiolabelled monoclonal antibodies.[49–53]

Radiolabelled peptides and other receptor-oriented ligands are getting increasing attention now since the availability of somatostatin analogs[34–36] such as octreotide (Octreoscan) and depreotide (NeoTect). These somatostatin analogs have been labeled with either ^{111}In or with ^{90}Y. While ^{111}In octreotide is available for diagnostic nuclear imaging of NET tumours, therapy with the same, but using larger doses of ^{111}In is available for clinical trials, but not yet FDA approved. ^{90}Y octreotide is also available for clinical trials of NET therapy. The results to date are promising for patients with a wide range of metastatic NET, including carcinoid tumours and gastrinomas, as well as neurofibromatosis.[34,54] For pheochromocytoma, however, ^{131}I labelled MIBG seems to be more effective and is certainly the more established form of therapy; though it is still not available commercially.

Clinical acceptance of radiolabelled antibodies will certainly increase with time as oncologists come to accept the limitations of chemotherapeutic agents and external radiation in curative and palliative roles. New antibodies are bio-engineered at a rapid rate and used for therapy trials.[55] The paper[1] in this issue of the Journal, therefore, is significant in furthering the acceptance of this mode of therapy in Oman. With more choices in radionuclide therapy available to the clinician for local and systemic uses to palliation and definitive therapy, it is high time to reconsider. We, as clinicians, need to look afresh at the expanding options that are now either offered in the market or are available for clinical trials. We need to lower our threshold of acceptance and appreciate these methods and what they can offer to our patients. Radionuclide therapy is effective, safe and cost effective, and deserves consideration earlier in the management of cancer patients rather than being left as a terminal choice. Its clinical acceptance is overdue.

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****Editor's note:** Prof. Lamki submitted this new reference, which appeared in print just after the galley proofs were approved..