

Radiopharmaceutical therapy in the new millenium.

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Many of us believe the roots of Nuclear Medicine are as much therapeutic as diagnostic – the “first Nuclear Medicine radionuclide”, iodine-131, was explored in thyroid disorders at about the same time to interrogate pathophysiologic features and therapeutic utility, a forerunner to the current theranostic paradigm.

Iodine-131 (I-131) therapy however remains as much an art as a standardized procedure. Therapy with I-131 – for hyperthyroidism as much as for thyroid cancer – is variable across institutions, with consideration being paid to logistic issues and convenience in addition to possible adverse effects and efficacy (1). This may be a function of both the large therapeutic window and the relatively benign natural course of these diseases.

Increasing cost constraints and the consequent reluctance on the part of institutional payors now necessitates greater rigor and standardization. Radiopharmaceutical therapy in cancer needs approval in a manner comparable to that for any other oncologic therapy, with hard measures of efficacy and strict regimens of therapy that specify radioactivity amounts and administration schedule.

Randomized phase III trials are thus perhaps a prerequisite for FDA approval. Samarium-153 EDTMP ([153Sm]-lexidronam, Quadramet®) and radium-223 dichloride (Xofigo®) approvals both followed rigorous demonstration of subjective (pain control) and objective (survival) improvement, respectively, compared to a statistically meaningful control population (2, 3).

Comparable rigor in the therapy trial of Gastro-Entero-Pancreatic NeuroEndocrine Tumors (GEPNET) using a lutetium-177 labeled peptide ([177Lu]-DOTATATE, Lutathera®) targeting a somatostatin receptor subtype (4) resulted in priority review of the agent by the FDA. The FDA was responsive to health care needs and facilitated an Expanded Access program to gather more efficacy data that enabled agent approval (5).

For several decades, neuroendocrine tumors that over-express norepinephrine transporter have been treated with iodine-131 labeled to a norepinephrine analog, benzylguanidine. The resultant compound – *meta*-iodo-benzylguanidine (or [131I]-mIBG) has been used outside the USA, much like radioiodine therapy, in a schedule determined both by efficacy and logistics (6). Efforts to enhance availability and utilization of this therapy were perhaps inevitable given the demonstrated efficacy of this therapy in a theranostic setting, exemplified by imaging to confirm biodistribution and tumor targeting followed by therapy with a large radioactive amount. Edward Coleman at Duke University led the systematic evaluation of [131I]-mIBG therapy in adult NET, and the article by Kane et al in the *Journal* (7) continues that fine tradition.

This retrospective review demonstrated significant symptom relief and survival benefit in 211 patients treated with [131I]-mIBG for metastatic neuroendocrine tumors at Duke University Hospital from 1991-2014. It confirms what the community has known for quite a while: I-131 mIBG therapy results in symptom improvement, and a delay in tumor growth, in a

substantial proportion of treated patients. (Improvement over existing therapy could only be suggested in this retrospective review without a matched control.)

The article also points out the need for continuing rigor in clinical conduct for all radiopharmaceutical therapies. The authors point out that “In particular, future studies would benefit from more consistent documentation of performance status in the clinical record, as well as the use of [an] objective index of general wellness in order to separate the influence of multiple therapies independent of the propensity to survive.” There are several such indices, and their application is routine in most oncology practice (8).

The authors end their Discussion by pointing out the weaknesses – largely involving missing data regarding patient status – that preclude greater confidence in the conclusions of their study. That experience should act as a cautionary tale that guides our clinical conduct – we need to adopt the highest oncology practice standards to evaluate our radiopharmaceutical therapies and enable them to be approved, accepted and utilized as an integral therapeutic option for an increasing number of diseases. We need to become as facile as recording patient performance scores and hematopoietic indices as we are at recording administered radioactivity amounts or absorbed doses.

Nuclear Medicine incorporates chemistry, physics, biology and instrumentation, among other broad fields of knowledge. Clinical Nuclear Medicine needs to incorporate other imaging as well as therapeutic modalities, to optimize utilization of the manifold ways in which this exciting discipline impacts health care, particularly in cancer. Our discipline is not a part of some other but rather a whole that is greater than the sum of its myriad parts (themselves components of other specialties and scientific fields).

Nuclear Medicine physicians have two broad clinical responsibilities: We evaluate images of *in vivo* radiopharmaceutical distribution to make clinical decisions. We also treat patients with therapeutic radiopharmaceuticals, bringing to bear our understanding of (molecular and clinical) radiochemistry, biology and pathophysiology. Our unique molecular imaging capabilities need to be combined with morphologic imaging (“conventional imaging”) to provide insight into pathophysiologic processes, and thus Nuclear Medicine physicians need to be well versed in *all* aspects of *in vivo* imaging. Only thus are we able to gain the confidence of referring clinician and patient alike.

We must similarly be well versed in *all* aspects of radiopharmaceutical therapy, not just those that relate to radiation safety and toxicity. We need to *take care* of our patients – administer the radiopharmaceutical, and also consider possible methods to ameliorate toxicity or enhance efficacy with other treatment modalities, working closely with our patients as well as our clinical colleagues. We need to be clinicians, expert in all aspects of patient care; this warrants our rigorous attention to clinical practice and management. The only way we will enable optimum utilization of our therapeutic arsenal is by becoming accepted as clinicians by our clinical colleagues.

References

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