U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes

Subcommittee on Emerging Radiopharmaceutical Therapy Knowledge Requirements in Theranostics

Final Report
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Subcommittee Charge:

The Subcommittee was formed in May 2021, by Dr. Darlene Metter, Chair of the Advisory Committee on the Medical Uses of Isotopes (ACMUI) to:

- To outline the knowledge and specific or specialized practice or policy requirements needed for the safe use and handling of emerging radiopharmaceuticals in theranostics.

- Provide considerations and recommendations to staff.

The Subcommittee reviewed the relevant literature (see reference section) and met virtually four times in July and August 2021 to discuss the charge and propose several considerations in consultation with the NRC staff.

Introduction:

Theranostics is the systemic integration of diagnostic tools (e.g., nuclear imaging) and therapeutic agents (e.g., radiopharmaceuticals) targeted to the same (or similar*) biomolecule (or physiologic parameter*). This concept is the fundamental foundation for precision medicine that has advanced considerably in view of our enhanced understanding of biology, developments in diagnostic technologies, and expansion of therapeutic options. Precision (or personalized) medicine is hoped to improve patient outcome. While theranostics may be applied to a variety of diseases, cancer has been the primary focus in this field (1-4).

Theranostics is a recent term, but it has long been a major player in the history of nuclear medicine, and the list and interest in use of theranostics have been increasing. Early example of theranostics dates back to 1941 when Dr. Saul Hertz from Massachusetts General Hospital, in Boston, MA, treated a patient with Graves' disease realizing that radioiodine can target the thyroid tissue based on the basic knowledge that thyroid gland concentrates iodine.

The list below are the currently clinically available theranostics imaging-therapy companion agents, with the biological and disease targets shown in the parenthesis:

- ^{123}I/^{131}I (NaI symporter; thyroid)
- ^{111}In-/^{90}Y-ibritumomab (anti-CD20; lymphoma)
- ^{18}F-NaF/^{99m}Tc-MDP; $^{223}RaCl_2$ (osteoblastic metastasis; mCRPC)*
- ^{99m}Tc-MAA; ^{90}Y-microspheres (hyperperfusion; liver tumors)*
- ^{123}I-/^{131}I-MIBG (norepinephrine transporter; pheochromocytoma, paraganglioma)
- ^{68}Ga-/^{64}Cu-DOTATATE, ^{68}Ga-DOTATOC; ^{177}Lu-DOTATATE (SSTR+ neuroendocrine tumors

NaI=sodium iodide, CD20=cluster of differentiate 20, mCRPC=metastatic castration-resistant prostate cancer, NaF=sodium fluoride, MAA=macroaggregated albumin, MDP=methyl diphosphonate, MIBG=meta-iodobenzylguanidine, DOTA= 1,4,7,10-tetraazacyclododecane-N,N',N",N""-tetraacetic acid, DOTATOC=DOTA-d-Phe1-Tyr3-octreotide, DOTATATE= DOTA-DPhe1,Tyr3-octreotate

In the near future, theranostics based on prostate specific membrane antigen (PSMA) will be available clinically for the imaging evaluation of prostate cancer (initial staging, biochemical recurrence) and radioligand therapy of metastatic castration-resistant prostate cancer. The imaging agents ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (Pylarify^{TM}) were approved by the FDA in December 2020 and May 2021, respectively. The favorable results of the randomized phase III VISION clinical trial on the therapy companion – ^{177}Lu-PSMA-617 – has recently been published in the New England Journal of Medicine facilitating an anticipated FDA approval within Q1 of 2022 (5).

Additional theranostics pairs are in the horizon within the next 7 years. These include the following companion agents with the biological and disease targets shown in the parenthesis:

- ^{225}Ac-/^{227}Th-PSMA (alpha RLT; mCRPC)
- ^{68}Ga-pentixafor/^{177}Lu-, ^{90}Y-pentixather (chemokine receptor 4; multiple myeloma)
- ^{68}Ga-/^{177}Lu-NeoB (GRPR; solid tumors)
- ^{68}Ga-/^{177}Lu-FAPI (fibroblast activation protein; multiple cancers)
- ^{89}Zr-/^{177}Lu-girentuximab (carbonic anhydrase IX; clear cell RCC)
- ^{68}Ga-/^{177}Lu-FF58 (integrin a_3b_5; GBM)
- ^{18}F-/^{131}I-PARPi (DNA repair enzyme Poly-(ADP ribose) polymerase 1; multiple cancers)

RLT=radioligand therapy, GRPR=gastrin-releasing peptide receptor, FAPI=fibroblast activated protein inhibitor, RCC=renal cell carcinoma, GBM=glioblastoma multiforme

Challenges:

Despite being a rapidly developing field, theranostics faces several challenges that will need to be addressed adequately in order for it to be fully integrated into clinical medicine (3).

- Technical Challenges:
  Need for standardized and efficient protocols; formation of interdisciplinary teams; incorporation into clinical guidelines; education and training.

- Economic challenges:
  Investment into supporting the supply chain for a steady pipeline of radioisotopes relevant to theranostics; sufficient reimbursement; comparative cost-utility analysis; Research and Development funding.

- Biomedical Challenges:
  Additional basic science, pre-clinical, first-in-human, and large prospective clinical trials; evaluation of single, tandem, and combination therapies; development of new applications in oncology and non-oncology arenas.

Subcommittee Specific Comments:

1) Radiopharmaceutical (RPT) Healthcare Team:
   Depending upon the therapy, the healthcare team administrating the RPT dose may consist of the Authorized User (AU) with appropriate training in theranostics, Certified Nuclear Medicine Technologist (CNMT), Registered Nurse, Radiation Safety Officer (RSO), and Medical Physicist (if available/applicable).

2) Authorized User responsibilities:
   AU should be present, either virtually or in person, at the time of dose administration; AU is responsible for patient concerns related to RPT, including radiation induced injuries; AU is encouraged to avail themselves of all the latest training information for each new theranostics as they emerge.

3) Radiation safety issues:
   Non-radiation workers of the healthcare team (e.g. oncology nurse) participating in the procedure may need to wear radiation badges for monitoring as determined by the RSO; therapy should be done in a dedicated and regulatory-approved room appropriate for radioisotope administrations (see Fig. 1); extravasation; patient release criteria (these issues are addressed by other ACMUI subcommittees).

4) Regulatory issues:
   Radioactive waste management (refer to the facility established guidelines and regulations); ensure that emerging theranostics are performed within the regulatory guidelines.

5) Dosimetry:
   Dosimetry-based (as opposed to fixed-activity) may play an increasingly important role (6-10); dosimetry-based approach may optimize patient outcome while minimizing

radiation toxicity; no randomized controlled trials to provide level 1 evidence for benefits of dosimetry-based approach; research is needed on impact of combined other nonradioactive therapy agents on RPT biodistribution and radiosensitivity, standardization across clinics, software and medical physicists, development of robust methodology for challenges of surrogate-imaging, microscale radiation effect and daughter distribution (relevant for alpha particles), and research on potential patient benefit versus cost and complexity of logistics; as relevant data becomes mature, AUs should stay abreast of developments in dosimetry.

6) Other relevant issues:
Outreach to AUs, healthcare providers, and patients to promote accurate information about safety and efficacy of theranostics (11).

Fig. 1. An illustrative example of a Radiopharmaceutical Therapy clinic room; an attached bathroom is to the left of the picture (not shown).

References:

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(4) Gomes Marin JF, et al. Theranostics in nuclear medicine: Emerging and Re-emerging Integrated Imaging and Therapies in the Era of Precision Oncology. Radiographics 2020; 40:1715-1740.
(5) Sartor O, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2021; 385:1091-1103.
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(10) SNMMI ^{177}Lu Dosimetry Challenge 2021. J Nucl Med 2021; 62:10N.
(11) SNMMI Theranostics Video: https://www.youtube.com/watch?v=Bb8Ts5HWS40

The ACMUI unanimously approved this report and its recommendations during its fall 2021 meeting on October 4, 2021.

Respectfully Submitted on October 14, 2021,
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