Published in final edited form as:

Health Phys. 2019 February ; 116(2): 175–178. doi:10.1097/HP.0000000000001000.

RADIOPHARMACEUTICAL THERAPY

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Abstract

Radiopharmaceutical therapy (RPT) involves the use of radionuclides that are either conjugated to tumor-targeting agents (e.g., nanoscale constructs, antibodies, peptides, and small molecules) or that concentrate in tumors through natural physiological mechanisms that occur predominantly in neoplastic cells. In the latter category, radioiodine therapy of thyroid cancer is the prototypical and most widely implemented RPT. In the category of radionuclide-ligand conjugates, antibody and peptide conjugates have been studied extensively. The efficacy of RPT relies on the ability to deliver cytotoxic radiation to tumor cells without causing prohibitive normal tissue toxicity. After some 30 y of preclinical and clinical research, a number of recent developments suggest that RPT is poised to emerge as an important and widely-recognized therapeutic modality. These developments include the substantial investment in antibodies by the pharmaceutical industry and the compelling rationale to build upon this already existing and widely-tested platform. In addition, the growing recognition that the signaling pathways responsible for tumor cell survival and proliferation are less easily and durably inhibited than originally envisioned has also provided a rationale for identifying agents that are cytotoxic rather than inhibitory. A number of radiopharmaceutical agents are currently undergoing clinical trial investigation; these include beta-particle emitters, such as ^{177}Lu , that are being used to label anti-somatostatin receptor peptides for neuroendocrine cancers and also prostate-specific membrane antigen targeting small molecules for prostate cancer. Alpha-particle emitting radionuclides have also been studied for RPT; these include ^{211}At for glioblastoma, ^{225}Ac for leukemias and prostate cancer, ^{212}Pb for breast cancer, and ^{223}Ra for prostate cancer. The alpha emitters have tended to show particular promise and there is substantial interest in further developing these agents for therapy of cancers that are particularly difficult to treat.

Keywords

National Council on Radiation Protection and Measurements; radiopharmaceutical therapy; beta-particle emitters; alpha-particle emitters

Radiopharmaceutical therapy (RPT) involves the targeted delivery of radiation to tumor cells or to the tumor microenvironment. This treatment approach is distinguished from external beam radiotherapy and brachytherapy in that the radiation is delivered by unencapsulated

radionuclides. RPT agents are systemically (in some cases, also locally) administered and localize to the tumor or its microenvironment. Tumor localization may occur because the radioactive element is involved in relevant tumor-associated biological processes or because the radionuclide is conjugated to a delivery vehicle that confers tumor targeting. Alternatively, passive accumulation due to physiologic mechanisms (e.g., enhanced permeability and retention) may provide targeting. Delivery vehicles that have been investigated include: microspheres, nanoparticles, antibodies, peptides, small molecules, and various constructs of each of these. RPT provides the advantage of beta and Auger electron as well as alpha-particle delivery directly to the targeted cell population. The principal drawback to RPT is that delivery cannot be externally controlled in the way that external beam radiotherapy and brachytherapy may be controlled.

The prototypical RPT, and perhaps the most effective treatment for metastatic cancer, is radioiodine therapy of thyroid cancer. Differentiated thyroid cancer metastases retain the ability to concentrate iodine for thyroglobulin hormone production. High activities of radioiodine (^{131}I) may be delivered via this mechanism leading to tumor cell death by beta particle irradiation. A more recent Food and Drug Administration (FDA) approved RPT, that also concentrates by an endogenous mechanism, is XofigoTM (^{223}Ra), an alpha-particle emitter that acts as a calcium mimetic and accumulates in blastic bone matrix (i.e., bone matrix that is rapidly being deposited) associated with prostate cancer metastases to bone (Parker et al. 2013).

Within the cancer therapy armamentarium, RPT is a treatment modality that shares features of both chemotherapy and targeted biologic therapy (Table 1). Like chemotherapy and in contrast to targeted biologic therapy which primarily inhibits signaling pathways associated with malignancy, RPT kills cells. Unlike chemotherapy, cell killing is based on the expression of tumor-specific markers rather than proliferation.

The number of RPTs available or under investigation has been increasing for the past several years (Table 2). The FDA approval and market success of XofigoTM demonstrated that alpha-emitter based RPTs (α RPT) can be successful. RPT using beta particle emitters (e.g., ^{131}I , ^{177}Lu , ^{90}Y) have accumulated a substantial clinical experience but much of this has been outside of rigorous clinical trials. This has made their efficacy relative to other treatment modalities difficult to judge. However, the preponderance of positive clinical outcomes when other treatment options have been exhausted has prompted pharmaceutical companies to initiate FDA registration trials towards commercialization of these agents. The recent FDA approval of ^{177}Lu -labeled anti-somatostatin peptide RPT, LutatheraTM, for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors is one such example (Strosberg et al. 2017).

All of the RPTs listed on Table 2 may be imaged. In some cases, a surrogate of the therapeutic agent may be used for imaging. Imaging may be used to evaluate tumor accumulation of the RPT, to assess early response to therapy by evaluating the reduction in RPT tumor accumulation, and to perform dosimetry calculations for patient RPT treatment planning. Dosimetry for RPT requires quantitative evaluation of the agents' biodistribution over time. A three-dimensional (3D) imaging method such as single-photon computed

tomography, combined with computed tomography (SPECT/CT) (Dewaraja et al. 2012, 2013; Ljungberg et al. 2016) and a dosimetry calculation that accounts for differences in tissue density and RPT nonuniformity for the treated patient (Kolbert et al. 2007; Prideauz et al. 2007; Hobbs et al. 2009; Dewaraja et al. 2010; Dieudonne et al. 2010; Senthamizhchelvan et al. 2012) provides the highest level of quantitative accuracy needed for RPT dosimetry and therefore the greatest likelihood that the dosimetry calculation will relate to biological outcome (organ toxicity or tumor control).

A 3D imaging-based dosimetry approach may also be used to plan combination RPT and external beam radiotherapy (Bodey et al. 2003, 2004; Hobbs et al. 2011a). The possibility of planning a treatment that combines complementary RPTs such as short-range α RPT with beta-particle RPT or with RPTs that have different half-lives and pharmacokinetics would also require patient-specific imaging-based treatment planning dosimetry (Hobbs et al. 2013). Although one might expect that imaging-based dosimetry would be limited by the resolution of the imaging instrumentation, it is possible to overcome this limitation. By combining imaging-based patient measurements with idealized model representations of the anatomy derived from a priori knowledge, the scale of the absorbed dose calculation need not depend upon the resolution of the anatomical imaging modality. An example of this is provided by imaging-based dosimetry of the arterial wall absorbed dose in lymphoma patients (Hobbs et al. 2010). By pairing human imaging-based measurements with preclinical microscale measurements of the activity distribution, the same conceptual approach leads to a macro-to-micro method that can provide absorbed dose estimates to microscale structures (Hobbs et al. 2012).

Fig. 1 summarizes how radiobiology may be coupled with patient imaging and with the dosimetric techniques referenced above to implement RPT therapy on a dosimetry-driven treatment planning basis rather than the empirically driven approach that must necessarily be adopted in chemotherapy and biologic therapy.

Acknowledgments and Conflicts of Interest

Work supported by NIH/NCI grants R01 CA116477. Dr. Sgouros is founder of Rapid, LLC, a dosimetry services startup. His involvement with this company is managed according to Johns Hopkins conflict of interest policies.

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Treatment Planning Paradigm

Fig. 1.

In a treatment planning approach to RPT delivery, data from imaging (e.g., using a pre-therapy tracer study) may be combined with a priori information regarding target and normal organ tissues (“other input”) to obtain a number of dosimetry parameters [e.g., the tolerance dose expressed in biologically effective dose (BED)] for a 3D dosimetry [e.g., using 3D-RD (Prideaux et al. 2007; Hobbs et al. 2008; Sgouros et al. 2008)] calculation that may provide a number of dosimetric parameters, including absorbed dose (AD), BED, and equivalent uniform dose (EUD) (Niemierko 1997; Hobbs et al. 2011b) so that the administered activity (AA) for tumor kill or for the dose-limiting tissue (DLT) may be calculated and then used to treat to normal organ tolerance or tumor kill.

Table 1.

Features of RPT relative to chemotherapy and biologic therapy.

Current cancer therapies

After the cancer has spread/metastasized

- Chemotherapy -Kill rapidly proliferating cells
 - Kill rapidly proliferating cells
- Radiopharmaceutical Therapy-Kill targeted cells by localized radiation delivery
 - Kill targeted cells by localized radiation delivery
- Targeted Biologic Therapy (hormonal Tx)
 - Inhibit signaling pathways that tumor cells are addicted to (i.e., rely on to maintain cancer phenotype)
- Immunotherapy
 - Overcome immune tolerance to cancer

Table 2.

RPT agents that are available or under investigation

RPT agent	Company	Indication
¹³¹ I-radioiodine	Malincrodt/Jubilant Draximage	Thyroid cancer
¹³¹ I -MIBG	Progenics	Adrenergic ⁺ tumors
²¹² Pb-trastuzumab	ArevaMed	HER2 ⁺ tumors
²¹² Pb -aSSR	ArevaMed/Radiomedix	Somatostatin ⁺ tumors
²¹² Pb -aTEM1	ArevaMed/Morphotek	TEM1 ⁺ tumors
²¹² Pb -aCD37	ArevaMed/NordicNanovector	Leukemia
¹³¹ I -aCD45	Actinium Pharmaceuticals	BM xplant prep
²²⁵ Ac-aCD33	Actinium Pharmaceuticals	Leukemia
⁹⁰ Y-microspheres	Varian/Sirtex	Hepatic malignancies
⁹⁰ Y -microspheres	BTG	Hepatic malignancies
Lutathera (¹⁷⁷ Lu)	Novartis/AAA	Somatostatin ⁺ tumors
¹⁷⁷ Lu -aPSMA-R2	Novartis/AAA	Prostate, tumor neovasc.
¹⁷⁷ Lu -NeoBOMB1	Novartis/AAA	Bombesin ⁺ tumors
Xofigo (²²³ Ra)	Bayer	Bone mets
HER2-TTC (²²⁷ Th)	Bayer	HER2 ⁺ tumors
PSMA-TTC (²²⁷ Th)	Bayer	Prostate, tumor neovasc.
MSLN-TTC (²²⁷ Th)	Bayer	Mesothelin ⁺ tumors
CD22 TTC (²²⁷ Th)	Bayer	Lymphoma
FPX-01 (²²⁵ Ac)	J&J/Fusion Pharma	NSCLC, pan-cancer target