Radionuclide Therapy: History, Present and Future Promise

Bennett S. Greenspan, MD, MS
Professor, Dept. of Radiology, MCG / AU
President, SNMMI
AAPM Annual Meeting, Denver, CO
History Symposium 8/02/2017

AUGUSTA UNIVERSITY

History of Radionuclide (RN) Therapy

- Disclosures: None

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- Learning Objectives:
- 1. Discuss the physiological basis and use of I-131 for treatment of hyperthyroidism and for papillary/follicular thyroid cancer.
- 2. Discuss the use of somatostatin receptor-targeted therapy for neuroendocrine tumors.
- 3. Discuss how beta and alpha emitters may be used, possibly in various combinations.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- Learning Objectives that are more appropriate:
- 1. Be able to discuss the dosimetry involved in determining optimal I-131 therapy for Graves' Disease.
- 2. Be able to discuss types of emissions, maximum energy and maximum range in tissue of various therapeutic radionuclides.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- The first radionuclide treatment was of P-32 sodium phosphate by John Lawrence in 1936 for leukemia, and shortly thereafter by Hamilton in 1936 for treatment of polycythemia rubra vera.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- I-131
- Saul Hertz, M.D. first used I-131 (mixed with I-130) in 1941 to treat a patient with Graves' Disease.
- 1942 – presentation of results in first 10 pts
- He initially treated a series of 29 patients. The results were published in a 5-year follow up in JAMA in 1946. 20 of 29 were cured.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- I-131 is the first theranostic agent.

- Saul Hertz –
- First use of radioiodine
- First radioiodine studies of metabolism
- First radioiodine treatment of hyperthyroidism - 1941
- First radioiodine treatment of thyroid cancer - 1942

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- 1951 – 1952 William Beierwaltes
- First successful radioimmunotherapy for cancer – in a patient with metastatic melanoma.
- 27 mCi of I-131 labeled antibodies
- Lesions disappeared and no recurrence for 9 years, when patient died from a car accident (autopsy revealed no malignancy).

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- Giants in Development of RN therapy
- Paul Ehrlich – idea of the "magic bullet"
- Saul Hertz – Father of radioiodine therapy
- William Beierwaltes – radionuclide therapy of endocrine diseases, especially thyroid
- Steve Larson – first Saul Hertz Award recipient at the 2016 SNMMI annual meeting

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- P-32 chromic phosphate for ovarian cancer, malignant ascites.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- 1980's : I-131 metaiodobenzyl guanidine (MIBG) was introduced for treatment of neuroendocrine tumors
- Somatostatin receptor-targeted therapy introduced to treat various solid tumors
- Introduction of radiolabeled antibodies to treat solid tumors

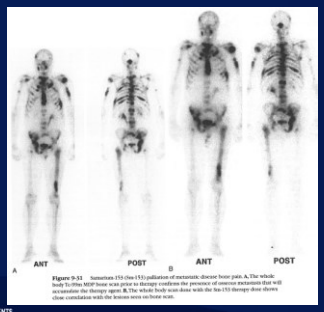
GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- 1980s: Bone pain palliation introduced.
- 1. Initially, P-32 sodium phosphate (also used for myeloproliferative disease) – No longer used due to possible side effects of pancytopenia and leukemia
- 2. Strontium-89 (Sr-89) chloride, 4 mCi given IV
- 3. Samarium-153 (Sm-153) EDTMP , 1.0 mCi/kg, given IV

GRU GEORGIA REGENTS UNIVERSITY

Bone pain palliation

- 

History of RN Therapy

- 1980s:
- I-131 lipiodol –hepatocellular carcinoma (hepatoma)

History of RN Therapy

- 1983
- Localization of I-131 p97-specific fragments in human melanoma as a basis for radiotherapy

History of RN Therapy

- Early 1980's I-131 meta-iodobenzyl guanidine (I-131 MIBG) - invented by William Beierwaltes
- For neural crest tumors, including neuroblastoma, malignant pheochromocytoma, paraganglioma, medullary thyroid carcinoma and carcinoid tumors
- 1999 – objective response (>50% tumor volume reduction) in approx. 50% of pts with neuroblastoma, pheochromocytoma and paraganglioma
- 2004 – Proven value in neuroblastoma, has a place in management of malignant pheochromocytoma

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- 1994 – First Peptide Receptor Radionuclide Therapy (PRRT) – In-111 octreotide – using Auger electrons (mean range <1 um)
- Neuroendocrine tumors – gastrinomas and other gastroenteropancreatic neoplasms, malignant carcinoid, pheochromocytoma and paraganglioma, Merkel cell carcinoma (a rare undifferentiated small cell carcinoma of the skin), and others

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- 1994 – First In-111 octreotide PRRT
- 1996 – First Yttrium-90 (Y-90) octreotide PRRT
- 1997 – First Y-90 DOTATOC PRRT
- 2000 – First Lu-177 octreotate PRRT
- Target - a somatostatin receptor on the cell surface of tumor cells. These therapies take advantage of the bystander effect.

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- Two agents (radiolabeled antibodies) were introduced to treat CD20 positive non-Hodgkin's lymphoma:
- 2002: Y-90 Ibritumomab Tiuxetan (Zevalin)
- 2003: I-131 tositumomab (Bexxar)

GRU GEORGIA REGENTS UNIVERSITY

History of RN Therapy

- A few benign conditions:
- First and foremost: I-131 therapy of hyperthyroidism (Graves' Disease, solitary autonomous nodule, toxic multinodular goiter)
- Radiation synovectomy, mainly for inflammatory (but non-infectious) processes, also for persistent effusion after knee prosthesis and for Baker's cyst

GRU GEORGIA REGENTS UNIVERSITY

Recent/Current List of Therapy Radionuclides

RN	T1/2	Emission	Max E (keV)	Max range (mm)
I-131	8 d	beta	610	2
Y-90	64 hr	beta	2280	12
Lu-177	6.7 d	beta	496	2
Cu-67	62 hr	beta	577	1.8
Re-186	91 hr	beta	1080	5.0
Re-188	17 hr	beta	2120	11.0
In-111	2.8 d	beta (auger)	19	<1
Sr-89	50.57 d	beta	1463	8
Sm-153	46.3 hr	beta	805	3.0

GRU GEORGIA REGENTS UNIVERSITY

Recent/Current List of Therapy Radionuclides

RN	T1/2	Emission	Max E (keV)	Max range (mm)
Ra-223	11.4 d	alpha	7500	<0.1
Bi-212	1 hr	alpha	8780	0.09
Bi-213	0.77 hr	alpha	>6000	<0.1
At-211	7.2 hr	alpha	7450	0.08
Ac-225	10 d	alpha(s)-4	5790(8380)	0.01
		beta(s)-3	1600	3
Tb-149	4.1 hr	alpha	3970	0.028

GRU GEORGIA REGENTS UNIVERSITY

Present

- I-131 sodium iodide – hyperthyroidism and papillary/follicular thyroid cancer
- Somatostatin receptor targeted therapy (also known as Peptide Receptor Radionuclide Therapy (PRRT) – for neuroendocrine tumors (NETs)
- I-131 MIBG for neural crest tumors, mainly neuroblastoma and malignant pheochromocytoma

GRU GEORGIA REGENTS UNIVERSITY

Present

- Radioimmunotherapy of lymphoma – using Y-90 ibritumomab tiuxetan targeting the CD20 receptor on the cell surface of non-Hodgkin's lymphoma
- Treatment of hepatic metastases (and also hepatocellular carcinoma) with Y-90 microspheres (glass beads or resin beads) by hepatic intra-arterial injection

GRU GEORGIA REGENTS UNIVERSITY

Present

- Radium-223 dichloride – approved in 2013 - for patients with castrate-resistant metastatic prostate carcinoma
- RN therapy for bone pain palliation, mainly Sm-153 EDTMP

GRU GEORGIA REGENTS UNIVERSITY

Present

- The following are currently being used in Germany:
- Y-90 DOTATATE
- Y-90 DOTATOC
- Y-90 DOTANOC

GRU GEORGIA REGENTS UNIVERSITY

Present

- Lu-177 DOTATATE for treatment of neuroendocrine tumors is now in clinical trials
- Lu-177 DOTATATE – midgut neuroendocrine tumors - NETTER-1 Trial

GRU GEORGIA REGENTS UNIVERSITY

Present

- I-131:
- Iodine is selectively taken up by the thyroid gland and incorporated into thyroid hormone
- Chemically, stable iodine (I-127) and I-131 (and other I isotopes) are identical
- I-131 is a beta-emitter and gamma-emitter (364 keV)
- T ½ = 8 days

GRU GEORGIA REGENTS UNIVERSITY

I-131 Sodium Iodide

- I-131 therapy for hyperthyroidism (toxic adenoma, multinodular goiter, and especially Graves' Disease) is effective, safe and inexpensive.
- I-131 is administered orally (by capsule or liquid form), and is rapidly and completely absorbed.
- I-131 is quickly concentrated, oxidized, and organified by follicular cells of the thyroid.
- Peak uptake generally occurs at approx. 24 hours.

GRU GEORGIA REGENTS UNIVERSITY

I-131 Sodium Iodide

- Ionizing effects of the beta emissions, which have a path length of 1-2 mm, destroy follicular cells, not only those cells that take up the I-131, but also adjacent follicular cells are irradiated, since the cell diameter is less than the path length of the beta emissions.
- An example of the bystander effect.

GRU GEORGIA REGENTS UNIVERSITY

I-131 Sodium Iodide - Dosimetry

- For thyrotoxicosis, 50 – 150 Gy (5,000 – 15,000 rad) generally will reduce hormone secretion to normal or below normal levels.
- For many years, 80 uCi/g (7,000 rad/g) was considered ideal for treatment of Graves' Disease.
- Currently, experts use 120-140 uCi/g .

GRU GEORGIA REGENTS UNIVERSITY

I-131 Therapy for Graves' Disease

- My preferred method:
- Delivered Radiation Dose Method

- Dosage (uCi) = cGy X Tp X est. gland weight (g)

  ---

  g-cGy/uCi I-131 X Teff X Max Uptake

Ref: Carol Marcus, Ph.D., M.D. UCLA

GRU GEORGIA REGENTS UNIVERSITY

I-131 Therapy Graves' Disease

- Delivered Radiation Dose Method - Example

- Dosage (uCi) = cGy X Tp X est. gland weight (g)

  12,000 8d e.g. 60 g

  ---------- = 20 mCi

  g-cGy/uCi I-131 X Teff X Max Uptake

  120 4d 0.6 (fractional = 60%)

Ref: Carol Marcus, Ph.D., M.D. UCLA

GRU GEORGIA REGENTS UNIVERSITY

I-131 Therapy for Thyroid Cancer

- Since papillary and follicular cell carcinomas function like normal thyroid, although less efficiently, they can be treated with I-131.
- Initial therapy is often 100 – 150 mCi.
- Remnant ablation can be achieved by 300 Gy (30,000 rad)

GRU GEORGIA REGENTS UNIVERSITY

I-131 Therapy for Thyroid Cancer

- Keep dose to bone marrow below 200 cGy (200 rad)
- In patients with miliary lung metastases, keep uptake by the lungs to less than 80 uCi (to avoid pulmonary fibrosis, a potentially fatal complication). Beierwaltes never observed lung uptake >40%; therefore, never treat with more than 200 mCi, and pulmonary fibrosis can be avoided.

GRU GEORGIA REGENTS UNIVERSITY

I-131 Therapy for Thyroid Cancer

- High level of controversy regarding:
- Optimal prescribed activity - empiric fixed-dose or not
- Adjuvant therapy
- Treatment of recurrence
- Metastatic disease
- Quantitative tumor and blood dosimetry

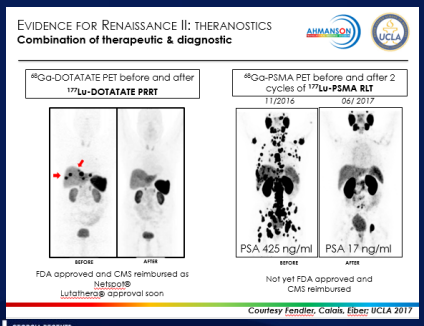
GRU GEORGIA REGENTS UNIVERSITY

Present/Future

- Lu-177 BPAMD therapy – endoradiotherapy of bone metastases
- Lu-177 CXCR4 and Y-90 CXCR4 - for multiple myeloma (theranostic agents with Ga-68 CXCR4)
- Lu-177 PSMA – RN therapy of metastatic castration-resistant prostate cancer

GRU GEORGIA REGENTS UNIVERSITY

Present/Future



GRU GEORGIA REGENTS UNIVERSITY

Courtesy of: Johannes Czernin, MD

Present/Future

GRU GEORGIA REGENTS UNIVERSITY

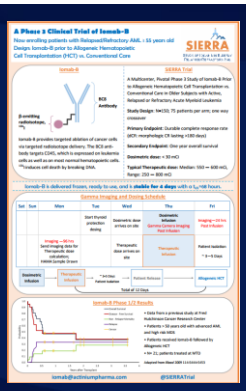
Courtesy of Richard Baum, MD

Present/Future

Phase 3 Clinical trial:

Radiolabeled antibody with I-131 for therapy of acute myeloid leukemia

Ref: David Gould, MD



GRU GEORGIA REGENTS UNIVERSITY

Present/Future

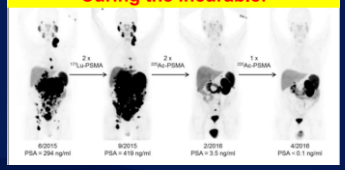
Moving Forward…Alpha Radiaton Therapy - the Coming Revolution

Alpha-radiation therapy with Actinium-225 labeled PSMA

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

Kratochwil et al. JNM 2016

Curing the incurable!



Courtesy of: Richard Baum, MD

GRU GEORGIA REGENTS UNIVERSITY

Present/Future

	Target	Indication
DIAGNOSTIC		
^{18}F-Fluciclovine (Axumin)	LAT	BCR Prostate CA
^{11}C-Choline	ChK	Prostate CA
^{68}Ga-DOTATATE (Netspot)	SSR	NET
^{18}F-Florbetaben (Neuraceq)	β-amyloid	Progressive NDD
^{18}F-Florpetapir (amyvid)	β-amyloid	Progressive NDD
^{123}I-Ioflupane (DATscan)	presynaptic DAT	Movement D.
THERAPEUTIC		
^{223}Ra-dichloride (Xofigo)	bone turnover	Bone met.
DIAGNOSTIC HOPEFULLY SOON		
^{68}Ga/^{18}F-PSMA	PSMA	Prostate CA
18F-Flurpiridaz	MC1	MPI
^{18}F-FDOPA	Presynaptic	Neurology, Oncology
THERAPEUTIC HOPEFULLY SOON		
^{177}Lu- DOTATATE	SSR	NET
^{177}Lu- PSMA/225Ac-PSMA	PSMA	Prostate CA

Other theranostic Pairs: Bombesin, CXCR4, Neurotensin; FOLATE Receptors; AB approaches

Courtesy of: Johannes Czernin, MD

GRU GEORGIA REGENTS UNIVERSITY

Present/Future of RN Therapy

- Tumor heterogeneity is a key factor limiting response to targeted therapy.
- Personalized (precision) medicine depends on biomarkers for selecting patients and directing radionuclide therapy.

Ref: modified from James Thrall, MD

GRU GEORGIA REGENTS UNIVERSITY

Future

- New targets, new ligands, improved peptides
- New radionuclides for imaging and therapy, including new alpha-emitters (possibly Ac-225, Bi-213, Tb-149)
- New combinations of RN therapy with other treatment modalities, especially immune modulation

Ref: Richard Baum, MD

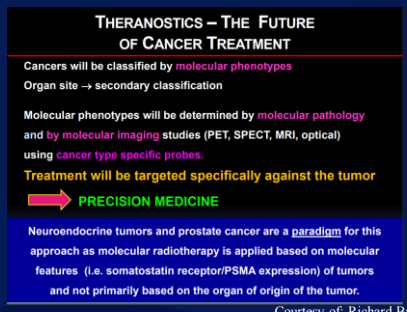
GRU GEORGIA REGENTS UNIVERSITY

Future

- RN therapy may include various combinations of alpha and beta emitters, to take advantage of different path lengths and energy levels, in combination with immune modulation and possibly also chemotherapy.
- However, RN therapy can take advantage of the bystander effect, which is not possible with chemotherapy.

GRU GEORGIA REGENTS UNIVERSITY

Future



- Courtesy of: Richard Baum, MD

GRU GEORGIA REGENTS UNIVERSITY

Future

- I predict that future developments in cancer therapy will include specifically targeted (precision) RN therapy, with targeting of various enzymatic pathways, and cell-surface receptors, including clonal variations. These RN therapies will also rely on precise dosimetry, probably including intralesional dosimetry. These RN therapies may include combinations of alpha and beta-emitters, which may provide more comprehensive therapy, and lead to less morbidity and much improved outcomes.

GRU GEORGIA REGENTS UNIVERSITY

Radionuclide Therapy: History, Present and Future Promise

- Thank you:
- Professor Dr. Richard P. Baum
- Johannes Czernin, M.D.
- Barbara Hertz
- James Thrall, M.D.

GRU GEORGIA REGENTS UNIVERSITY