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Safety Assessment for Radiotherapeutics

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Radiopharmaceuticals: Safety Considerations

- Acute toxicity
  - Hematologic, renal, hormonal (neuroendocrine tumors)
- Long-term toxicity
  - Hematologic, renal, **secondary malignancies**
- Risk mitigation
  - Safety monitoring and supportive care
  - Labeling
  - Post-marketing requirements

Recent Radiotherapeutic Approvals for Oncology Indications

Radium Ra 223 dichloride (XOFIGO®) 2013

for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease

- **3.6 month improvement in median OS; delay in time to first symptomatic skeletal event**

Lutetium Lu-177 dotatate (LUTATHERA®) 2018

for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults

- **Improved PFS: HR 0.21 (0.13, 0.32); improved median OS: HR 0.52 (0.32, 0.84)**

Iobenguane I-131 (AZEDRA®) 2018

for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy

- **25% of patients had anti-HTN meds dose reduced by at least 50% for at least 6 mo; ORR 22% (14, 33)**

Bone Marrow Toxicity

Acute/Subacute Hematologic Toxicity

- Bone marrow is radiosensitive and a dose-limiting organ
- Maximum absorbed dose of 2 Gy to BM
  - Potential binding of products to bone marrow stem cells
  - Cross-dose from source organs and tumors
  - Variation in bone marrow absorbed dose between patients
- Acute/subacute myelosuppression is generally tolerable
- Risk factors associated with grade 3 or 4 toxicity:
  - Age > 70 yrs
  - Prior chemotherapy
  - Creatinine clearance
  - Bone metastases

Radium Ra 223 dichloride: Hematologic Toxicity

- Safety data from 600 patients with metastatic CRPC with bone mets
- 58% of patients received prior docetaxel
- Median duration of treatment of 20 weeks (6 cycles)
- 13 patients (2%) experienced bone marrow failure
  - 2 fatal events
  - 7 patients had ongoing pancytopenia at time of death
  - 7 patients required transfusion support
- Permanent discontinuation in 4% of pts for anemia or thrombocytopenia
  - Grade 3-4 thrombocytopenia higher in patients who received prior docetaxel
- CBCs Q4 weeks prior to dose; nadir CBCs not well characterized
- Separate single-dose study showed neutrophil and platelet count nadirs at 2 to 3 weeks (doses 1 to 5 times recommended dose) and recovery at approximately 6 to 8 weeks

Radium Ra 223 dichloride: Hematologic Toxicity

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

Uncertainties: ability to tolerate concomitant or subsequent cytotoxic chemotherapy; optimal sequencing of treatments; disease related myelosuppression due to marrow infiltration

I-131 Iobenguane: Hematologic Toxicity

- Safety data from 88 patients with recurrent or unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma
  - Grade 3-4 thrombocytopenia: 50%
  - Grade 3-4 neutropenia: 59%; Grade 4=16%
  - Grade 3-4 anemia: 24%
  - Febrile neutropenia: 5%
- Blood count nadirs occurred 4 – 8 weeks following infusion
  - Median time to nadir: platelets - 4.3 wks, neutrophils - 5.4 wks, Hb: 6.7 wks
- Median time to recovery was 2 wks for platelets and neutrophils
- 24% of patients received red cell transfusions; 16% received platelets
- Approximately 9% required G-CSF and 3% received erythropoietin

Lutetium Lu-177 dotatate: Hematologic Toxicity

- NETTER-1: 223 patients with progressive, midgut carcinoid tumors randomized to Lu-177 dotatate (n=111) or LA octreotide (n=112)
- Myelosuppression was common

Laboratory Abnormality[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Hematology				
Lymphopenia	90	44	39	4
Anemia	81	0	54	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0

Longterm hematologic toxicity: Myelodysplasia and Leukemia

- Risk factors for chronic toxicity
  - Duration from first to last cycle of PRRT
  - Prior chemotherapy and/or RT
  - Platelet toxicity during PRRT
  - Tumor invasion of marrow
- Lutetium Lu-177 dotatate
  - NETTER-1 (n=111): 3% pts developed MDS
  - ERASMUS (n=811): 2% pts developed MDS
    <1% pts developed acute leukemia
- Iobenguane I-131
  - 6/88 (7%) developed MDS or acute leukemia at 9 months to 7 years
  - All patients received prior chemo or radiotherapy

Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with ^{177}Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors (Bergsma et al, Journal of Nuclear Medicine 2018)

TABLE 3
Characteristics of 11 of 274 GEP NET Patients with PHD after PRRT with ^{177}Lu-DOTATATE

Patient no.	Sex	Age (y)	Diagnosis	Previous therapy	Administered activity (GBq)	PRRT		BM		Latency period (mo)
						Interrupted	Protocol	Cytopenia	Diagnosis	
359	F	70	NET	Cold octreotide	30.0	No	On	Hb	MDS, RARS	42.4
297	F	60	NET	Cold octreotide	18.6	Yes, maximum kidney dose	On	Hb, PLT, WBC	Hypoplasia	36.3
293	M	61	PNET	Chemoembolization	29.3	No	On	Hb, PLT	CML	42.3
284	M	57	PNET	—	29.7	No	On	Hb	MDS, RAEB-II	33.3
252	F	64	NET	Cold octreotide	30.0	No	On	Hb, WBC	Pancytopenia	45.7
241	F	41	PNET	—	26.3	Yes, hematologic toxicity	On	Hb, PLT, WBC	Aplasia	34.3
185	M	74	PNET	—	26.4	No	On	Hb, PLT	MDS/MPN: CMML-1	63.6
158	M	62	NET	Cold octreotide	22.2	Yes, maximum kidney dose	Off	Hb, PLT, WBC	MDS, RAEB-II	15.4
102	M	68	NET	—	30.0	no	On	Hb, PLT, WBC	MDS, hypocellular	20.2
91	F	59	NET	Cold octreotide, local EBRT	22.7	Yes, maximum kidney dose	On	Hb, PLT, WBC	AML	83.5
81	F	58	NET	Cold octreotide	22.3	Yes, maximum kidney dose	On	Hb, PLT, WBC	Myelofibrosis/ MPN	40.8

PNET = pancreatic NET; EBRT = external-beam radiotherapy; Hb = hemoglobin; PLT = platelets; WBC = white blood cells; RARS = refractory anemia with ringed sideroblasts; CML = chronic myeloid leukemia; RAEB = refractory anemia with excess blasts; CMML = chronic myelomonocytic leukemia.

- **4% (11/274) patients developed PHD**
- **RR of 2.7** based on registry data
- Median latency period of 41 mo
- No correlation with gender, age, bone mets, prior chemotx, prior EBRT, renal fx, heme toxicity during PRRT

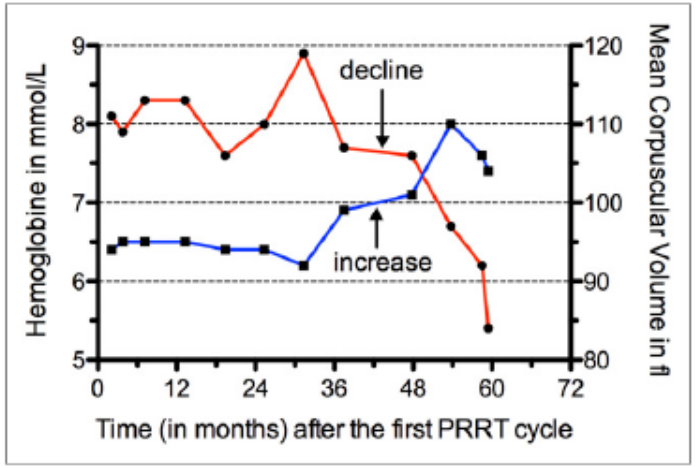

FIGURE 4. Course of hemoglobin (red) and mean corpuscular volume (blue) in patient 185, diagnosed with MDS/MPN after PRRT with ^{177}Lu-DOTATATE. Time zero is date of last PRRT cycle. Decline in hemoglobin was followed by increase in mean corpuscular volume (arrows).

Radiopharmaceuticals: Renal Toxicity

- Kidney uptake of radiopeptides can cause nephrotoxicity after PRRT.
  - Radiopeptides reabsorbed in the proximal tubule.
  - Renal retention causes a high radiation dose to kidneys.

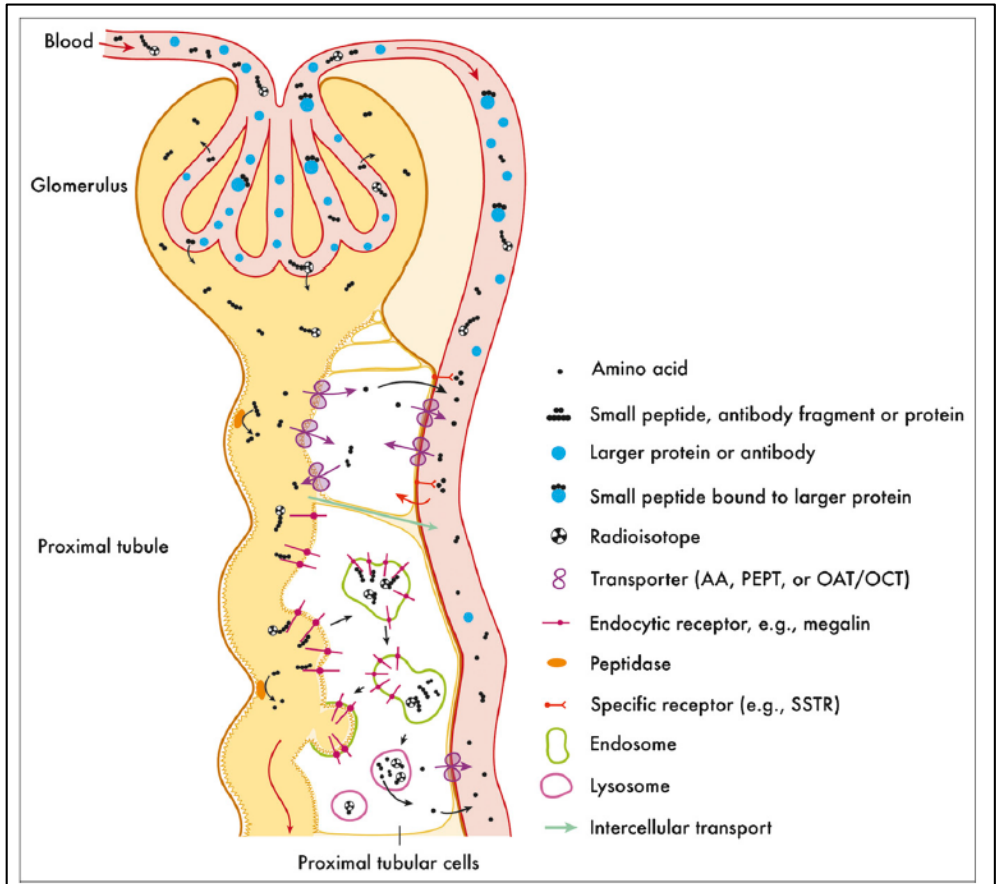

FIGURE 1. Overview of glomerular and proximal tubular handling of proteins and peptides. AA = amino acid transporter; OCT = organic cation transporter; PEPT = oligopeptide transporter.

Vegt 2010

Radiolabeled SSAs: Renal Toxicity

- Acute kidney damage occurs 2 weeks to 6 months after PRRT
- Chronic kidney damage less common
  - damage to glomeruli, tubular atrophy and interstitial fibrosis
- Risk factors: baseline anemia, HTN, diabetes
- Risk of radiation nephropathy dependent on the radionuclide
  - ^{90}Y-octreotide has higher energy emission and longer penetration range is than ^{177}Lu-octreotide
- Amino acid co-infusion-competitive inhibition at PT
- Lutetium Lu-177 dotatate (NETTER-1)
  - Gr 3-4 creatinine elevation was 1%
  - No meaningful difference between arms for creatinine or creatinine clearance at median follow up of 19 mos.

Neuroendocrine Tumors: Acute Hormonal Crises

- NETs have characteristic symptoms based on excessive and uncontrolled release of metabolically active substances
- Carcinoid crisis = medical emergency
  - Manipulation of a carcinoid tumor or pheochromocytoma - anesthesia, procedures, chemotx
  - Flushing, hypotension, extreme changes in BP, diarrhea, bronchoconstriction, arrhythmias
- "Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3] octreotate" (de Keizer, 2008)
  - 6/479 pts (1%) with GEPNET or pheochromocytoma experienced hormonal crises during cycle 1

Radiopharmaceuticals: Risk Mitigation

- Choice of radionuclide
- Eligibility criteria
- Individual dosimetry
- Safety monitoring during infusions
- Amino Acid coinfusion
- Supportive care
  - Antiemetics
  - Stem cell infusion protocols
- Sufficient safety follow-up

Risk Mitigation: Product Label

- Sections 2, 5, 6 - placeholder

Risk Mitigation: Post Marketing Requirements

- Objectives
  - To conduct further safety studies of patient populations at highest risk
  - To provide evidence-based dose modifications and monitoring recommendations
- PMRs for Radium Ra 223 dichloride
  - Observational safety study for general longterm safety
  - Randomized trial to assess risk of BM suppression and for secondary malignancies
  - Re-treatment study
- PMRs for Iobenguane I-131 and Lutetium Lu-177 dotatate
  - Requirement to submit cumulative safety analyses after 5 and 10 years of follow-up to characterize the risks of MDS, leukemia and other secondary malignancies
  - Lu-177 dotatate has a PMR to investigate longterm renal toxicity

Radiopharmaceuticals: an active drug development area

Table 2 | **Selected RPT agents that are on the market or under development**

RPT agent	Company	Indication	Properties	Development phase	NCT number	Refs
Radium-223 chloride*	Bayer	Bone metastasis	Calcium analogue	Commercially available	–	
^{90}Y-loaded glass microspheres	BTG	Hepatic malignancies	Radioembolization of liver microvasculature	Commercially available	–	
^{90}Y-loaded resin microspheres	CDH Genetech/ Sirtex	Hepatic malignancies	Radioembolization of liver microvasculature	Commercially available	–	
^{131}I radioiodine	Jubilant Draximage/ Mallinckrodt	Thyroid cancer	Active uptake through Na–I symporter and storage in follicular cells	Commercially available	–	
^{153}[Sm]lexidronam	Lantheus	Cancer bone pain	Binding to hydroxyapatite matrix	Commercially available	–	
^{177}Lu-labelled DOTATATE	Novartis/AAA	Neuroendocrine tumours	SSR-mediated binding	Commercially available	–	
[^{131}I]mIBG	Progenics	Adrenergic receptor$^+$ tumours	Active uptake mechanism via the adrenaline transporter and storage in presynaptic neurosecretory granules	Commercially available	–	
^{131}I-labelled aCD45	Actinium Pharmaceuticals	Bone marrow transplant preparation	^{131}I-based antibody targeting CD45$^+$ cells for bone marrow ablation before transplantation	Phase III; recruiting	NCT02665065	
^{177}Lu-labelled PSMA-617	Novartis/ Endocyte	Prostate cancer, tumour neovasculature	PSMA-mediated binding	Phase III; active, not recruiting	NCT03511664	
^{177}Lu-labelled NeoBOMB1	Novartis/AAA	GRPR$^+$ tumours	GRPR binding	Phase II; completed Phase I/II; completed	NCT03724253 NCT02931929	
^{166}Ho microspheres	Terumo	Hepatic malignancies	Radioembolization of liver microvasculature	Phase II; unknown recruitment status	NCT02067988	
^{177}Lu-labelled DOTA-JR11	Ipsen	Neuroendocrine tumours	SSR-mediated binding and internalization	Phase I/II	NCT02592707	
^{177}Lu-labelled PSMA-R2	Novartis/AAA	Prostate cancer, tumour neovasculature	PSMA-mediated binding and internalization	Phase I/II; recruiting	NCT03490838	
^{225}Ac-labelled aCD38*	Actinium Pharmaceuticals	Multiple myeloma	CD38 antibody α-targeting	Phase I; recruiting	NCT02998047	
^{225}Ac-labelled aCD33*	Actinium Pharmaceuticals	Leukaemia, MDS	CD33 antibody α-targeting	Phase I; withdrawn	NCT03705858	
^{227}Th-labelled MSLN-TTC*	Bayer	Mesothelin$^+$ tumours	Anti-mesothelin–α-emitter immunoconjugate	Phase I; recruiting	NCT03507452	
^{227}Th-labelled PSMA-TTC*	Bayer	Prostate, tumour neovasculature	PSMA-targeting α-emitter immunoconjugate; PSMA$^+$ prostate cancer targeting	Phase I; recruiting	NCT03724747	
^{227}Th-labelled aCD22-TTC*	Bayer	Lymphoma	Anti-CD22–α-emitter immunoconjugate; CD22$^+$ tumours (lymphoma)	Phase I; active, not recruiting	NCT02581878	
^{177}Lu-labelled CTT-1403	Cancer Targeted Technologies	Prostate, tumour neovasculature	PSMA-mediated binding	Phase I; active, not recruiting	NCT03822871	
^{131}I-labelled CLR131	Cellectar	Paediatric cancer, head and neck cancer, multiple myeloma, leukaemia, lymphoma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; recruiting Phase I; suspended (owing to COVID-19) Phase II; recruiting	NCT03478462 NCT04105543 NCT02952508	
^{131}I-labelled CLR1404	Cellectar	Unresponsive solid tumour, multiple myeloma	^{131}I-labelled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains	Phase I; not recruiting Phase I; completed	NCT02278315 NCT01495663	
^{225}Ac-labelled FPX-01*	J&J/Fusion Pharma	NSCLC, pan-cancer target	Insulin growth factor 1$^+$ tumours	Phase I; recruiting	NCT03746431	
[^{153}Sm]CycloSam	Oncolix/ Isotherapeutics	Osteosarcoma	Binding to hydroxyapatite matrix	Phase I; not yet recruiting	NCT03612466	
^{203}Pb-labelled DOTAMTATE*	OranoMed/ Radiomedix	SSR$^+$ tumours	SSR-mediated binding	Phase I; active, not recruiting	NCT03466216	
^{177}Lu-labelled RM2	ABX GmbH	GRPR$^+$ tumours	GRPR binding	First in human	–	
^{227}Th-labelled HER2-TTC*	Bayer	HER2$^+$ tumours	Anti-HER2–α-emitter immunoconjugate	Preclinical	–	
^{212}Pb-labelled PLE*	OranoMed/ Cellectar	Solid tumours	–	Preclinical	–	–
^{212}Pb-labelled aTEM1*	OranoMed/ Morphotek	TEM1$^+$ tumours	–	Preclinical	–	–
^{212}Pb-labelled aCD37*	OranoMed/ NordicNanovector	Leukaemia/ lymphoma	CD37 antibody α-targeting	Preclinical	–	–
^{211}At-labelled aLAT-1*	Telix Pharma	Multiple myeloma	–	Preclinical	–	–

Sgouros, Nature Reviews 2020

Summary

- Radiopharmaceutical development is an active and growing field for the targeted treatment of various cancers.
- Longterm toxicity must be considered in the benefit:risk assessment for radiolabeled products; prevention is key as some end organ toxicities may be irreversible.
- Standard clinical practices have evolved to safely administer radiopharmaceuticals while mitigating risk for acute and chronic radiation-associated toxicity.
- FDA recognizes the need for patient access to effective treatments and continues to work closely with sponsors to strategize on how to enhance dosing while minimizing radiation-associated toxicities.

Thank you