Journal of Nuclear Medicine, published on January 30, 2021 as doi:10.2967/jnumed.120.254987

Addition Of ^{131}I MIBG To PRRT (^{90}Y DOTATOC) For Personalized Treatment of Selected Patients with Neuroendocrine Tumors

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Word Count 2628

Financial Support Funding for this trial and support for the investigators was provided by The University of Iowa Department of Radiology, the Holden Comprehensive Cancer Center (3P30CA086862), and the Neuroendocrine SPORE (P50CA174521). The authors do not have a conflict of interest.

Running Title Preliminary results PRRT plus ^{131}IMIBG

Abstract

Introduction PRRT is an effective treatment for metastatic neuroendocrine tumors (NETs). Delivering sufficient tumor radiation dose remains challenging due to critical organ dose-limitations. Adding ^{131}I MIBG to PRRT may be advantageous in this regard.

Methods A phase 1 clinical trial was initiated for patients with non-operable progressive NETs using a combination of ^{90}Y DOTATOC plus ^{131}I MIBG. Treatment cohorts were defined by radiation dose limits to kidneys and bone marrow. Subject specific dosimetry was used to determine the administered activity levels.

Results The first cohort treated subjects to 1900 cGy kidneys and 150 cGy marrow. No dose limiting toxicities were observed. Tumor dosimetry estimates demonstrated an expected dose increase of 34-83% using combination therapy as opposed to ^{90}Y DOTATOC PRRT alone.

Conclusion These findings demonstrate the feasibility of using organ dose for a phase 1 escalation design and suggest the safety of using ^{90}Y DOTATOC and ^{131}I-MIBG.

Keywords personalized dosimetry, MIBG, PRRT, DOTATOC

Introduction

Peptide receptor radionuclide therapy (PRRT) either as ^{177}Lu DOTA-Tyr^{3}-octreotate (LUTATHERA®, Advanced Accelerator Applications) or ^{90}Y DOTA-tyr3-Octreotide (^{90}YDOTATOC), is well established as an effective form of treatment for patients with metastatic NETs (1-3). Delivering sufficient tumor radiation dose to result in a high percentage of overall response rates remains challenging due to limits imposed on administered activity levels by radiation induced normal organ toxicity (4). The critical organ for ^{90}Y DOTATOC which limits the amount of deliverable administered activity is typically the kidney (5,6). Targeted radionuclide therapy with ^{131}I metaiodobenzylguanidine (^{131}I MIBG) has also demonstrated promise in some patients with advanced stage neuroendocrine tumors (7,8). ^{131}I MIBG targets tumor sites in over 50% of patients with midgut NETs through a distinctly different mechanism compared to PRRT agents (9). The amount of administered activity that can be safely delivered is limited primarily by radiation to bone marrow as opposed to kidneys (10). We have previously demonstrated that this difference enables the combination of large fractions of each agent (relative to amounts that can be delivered safely alone/individually) into a single treatment regimen which results in higher total tumor radiation doses without exceeding dose limits for either the marrow or kidneys (11). Moreover, known differences in tumor distribution of MIBG and radiolabeled octreopeptides may prove advantages for combined therapy.

Traditionally, targeted radionuclide therapy cancer trials have relied on a “one size fits all” approach to treating patients in terms of prescribed levels of administered activity. This approach to radionuclide based therapy is considered by many to be less desirable than using personalized patient specific dosimetry to guide treatment (12,13). We initiated a phase 1 clinical trial whereby the escalation design was based on increasing the radiation dose limits to critical organs between cohorts as opposed to using cohorts defined by specific escalated levels of administered activity. Within this trial framework

we utilize the technique previously described for addition of ^{131}I MIBG to PRRT utilizing patient specific dosimetry (14). We report here the results from this trial prior to a redesign wherein ^{90}Y DOTATOC is being replaced by ^{177}Lu DOTATATE and low specific activity ^{131}I MIBG is being replaced by high specific activity ^{131}I MIBG.

Materials and Methods

The study was approved by the University of Iowa Biomedical Institutional Review Board (IRB-01) and all subjects provided documented (written) independent consent. Patients with non-operable (metastatic or local), progressive NETs of midgut origin with ^{68}Ga DOTATATE positive tumors on PET were invited to participate. Combined imaging with ^{111}In-pentetreotide (as a biodistribution surrogate for ^{90}Y DOTATOC) and ^{131}I-MIBG was performed in each subject for dosimetric analysis and detailed tumor targeting assessment. To be eligible to proceed to treatment, subjects had to demonstrate at least one of the following based upon results from the combined imaging/biodistribution studies:

- One or more MIBG+ and DOTATOC- tumors
- One or more tumor sites where the expected tumor radiation dose is higher by at least 25% with a combination of ^{90}Y DOTATOC plus ^{131}I-MIBG compared with ^{90}Y DOTATOC alone.

Imaging/Dosimetry

Imaging/blood sampling was performed at 1, 4, 24, and 48 hours following combined administration of 222 MBq of ^{111}In-pentetreotide plus 74 MBq of ^{131}I-MIBG. Planar and SPECT/CT images were acquired as multi-isotope studies with a 20% window on the 364-keV photopeak of ^{131}I and the 247 keV photopeak of ^{111}In. High energy collimation was used for all simultaneous imaging studies. Scatter correction was performed. Appropriate 1.85 MBq standards of ^{131}I and ^{111}In were placed within the field. Organ and tumor mass were measured from the CT. Dose determinations were performed for kidneys

and bone marrow and up to 2 soft tissue tumor sites per organ system. Marrow dosimetry was based on blood to marrow beta and organ/tumor to marrow gamma contributions. OLINDA v1.1 was used.

Therapy

Cohort 1 subjects were treated with a combination of ^{131}I MIBG and ^{90}Y DOTATOC administered activity (AA) in amounts calculated to deliver a total expected cumulative renal radiation dose of 1900 cGy and a bone marrow dose of 150 cGy (delivered over 2 equal treatment cycles separated by 10-12 weeks). The concept and methods to accomplish these AA calculations have been described previously (11,15). The trial escalation paradigm is depicted in Figure 1.

Each cycle consisted of ^{90}Y DOTATOC delivered as an outpatient (day 1) followed by in-patient ^{131}I MIBG infusion (day 2). A compounded amino acid solution containing 25 gm lysine and 25 gm arginine was administered with ^{90}Y DOTATOC infusion.

Blood counts, serum creatinine, and urinary protein were assessed regularly beginning at baseline through 6 months post-cycle 2 to evaluate for dose limiting toxicity. Dose limiting toxicities were based on CTCAE v4.03.

Results

Six patients consented to trial; of these, one subject did not meet the second phase eligibility criteria, a second had insurance deny clinical trial participation, and a third withdrew for personal reasons. There were 2 men and 1 woman in the cohort presented here ages 50-68. Tumor sites were located in liver and/or abdominal lymph nodes and in one case the anterior abdominal wall. The primary

tumor (small bowel in all cases) had been excised in each patient. None of the subjects had bone metastases.

In each of the 3 treated subjects, it was determined that over 300 mCi (total) of ^{131}I MIBG could be safely added to dosimetrically determined levels of ^{90}Y DOTATOC (Table 1). The pre-therapy tumor dosimetry results revealed that expected tumor dose increases could be achieved through addition of ^{131}I MIBG to ^{90}Y DOTATOC compared to what would have been the case for ^{90}Y DOTATOC given in maximum amounts alone. Calculated tumor dose increases through the addition of ^{131}I MIBG ranged from 34-83% in 5 of the 6 target tumors evaluated. An example of one of these tumors is depicted in Figure 2. The calculated expected tumor dose increase in the 6th tumor was an outlier at 362%.

No dose limiting toxicities were observed during the six-month DLT window. One subject did register a temporary grade 3 thrombocytopenia following the second cycle and another developed grade 2 kidney toxicity after therapy completion (creatinine 1.6) which remained stable at 1-year post treatment. Toxicity data are provided (Table 2). By RECIST 1.1 criteria all 3 subjects showed stable disease 6 months after cycle 2.

Discussion

Opening the trial was delayed for clinical trials CMS billing compliance review and approval; as the first study of its kind, the trial created a new billing pathway for radionuclide-based planning dosimetry. Enrollment was later hampered by the approval of ^{177}Lu-DOTATATE (LUTATHERA) which meant potential participants had to choose between an FDA-approved commercial therapy or an experimental phase 1 clinical trial. The trial reported here was designed 6 years ago at a time in the United States when the only available cationic amino acid

solution was highly emetogenic. Consequently, we did not wish to subject patients to an additional infusion of amino acids for the dosimetric evaluation phase of our trial. Thus to partially adjust for this, we applied a fixed 20% reduction to the ^{111}In-pentetreotide generated RT for use in estimating the expected ^{90}Y DOTATOC kidney dose for each subject (16). Because the effect of the lysine/arginine solution on renal octreopeptide uptake may vary substantially from one individual to another, we have revised the protocol to account for this going forward. Subject biodistribution data can be obtained in future cohorts following ^{177}Lu DOTATATE treatment (eliminating the need for the pretreatment ^{111}In-pentetreotide surrogate). Moreover, if biodistribution images are obtained following a therapeutic administration, the amino acid effect on renal uptake and radiation dose becomes patient specific. Finally, high specific activity ^{131}I MIBG (AZEDRA®) is now an approved agent. High specific activity ^{131}I MIBG may be expected to deliver higher tumor dose levels through improved initial tumor uptake yet with similar marrow and renal dosimetry compared to low specific activity MIBG (17). The revised trial design is depicted in Figure 3.

Conclusion

These results support the concept that adding ^{131}I MIBG to PRRT based on individual patient dosimetry can be performed safely and with the possibility of increasing delivered tumor dose beyond that achievable with ^{90}Y-DOTATOC PRRT alone.

Acknowledgements

The authors are deeply grateful for the important contributions made by the following individuals: Kristin Gamari-Varner, Jeff Murguia, Dan Peterson, Mary Schall, Veronica Howsare,

Phil Danzer and also Teresa Ruggle in the University of Iowa Design Center. In addition, the authors sincerely thank the clinical trial participants, their families, and the caregivers for making this trial possible.

Financial Disclosures

Funding for this trial and support for the investigators was provided by The University of Iowa Department of Radiology, the Holden Comprehensive Cancer Center (3P30CA086862), and the NCI Neuroendocrine SPORE (P50CA174521). The authors do not have a conflict of interest.

Disclaimer

None

Key Points

Question

What are the maximum tolerated critical organ dose limits for therapy with ^{131}I-MIBG added to PRRT (^{90}Y-DOTATOC)?

Pertinent Findings

Personalized combination of ^{131}I-MIBG added to ^{90}Y-DOTATOC, calculated to deliver 1900 cGy to the kidneys and 150 cGy to bone marrow, demonstrated no clinically significant toxicities. Tumors demonstrated an expected dose increase of 34-83% (with one outlier of 362%) using combination therapy. ^{177}Lu DOTATATE (LUTATHERA) will replace ^{90}Y DOTATOC and high specific activity ^{131}I-MIBG (AZEDRA) will replace low specific activity ^{131}I-MIBG in the next cohort.

Implications for Patient Care

Once maximum tolerated organ dose limits for this treatment paradigm are established, a phase 2 trial may be safely initiated.

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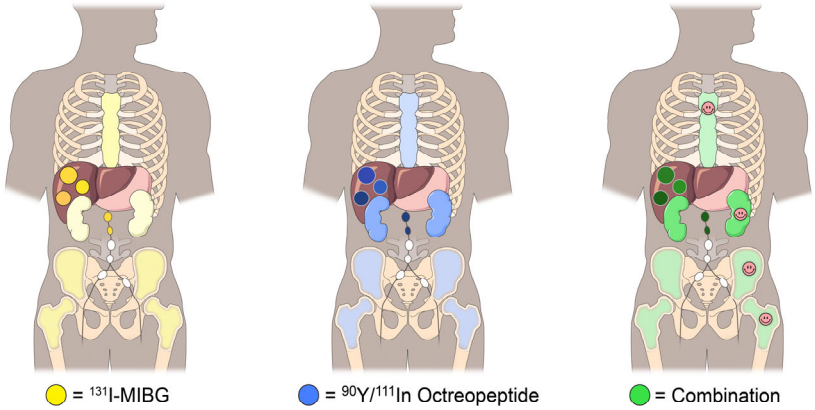
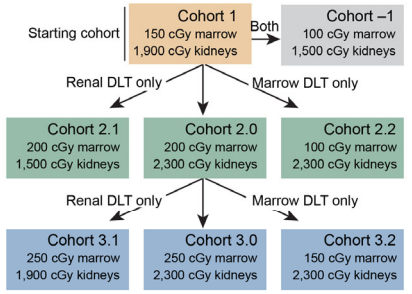
Graphic Abstract



Figures/Legends



Cohorts represent total dose administered 2 cycles 12 weeks apart

DLT frequency	Escalation or stopping rule
0 out of 3	evaluate 3 subjects in next cohort (2.0 or 3.0)
1 out of 3	evaluate 3 more subjects at this dose level: – if 0 out of 3 experience DLT, escalation continues – otherwise, dose adjust per renal / marrow / both
≥2 (both)	– dose escalation is stopped – this dose level is maximally administered dose
≥2 (renal only)	– dose adjust to appropriate renal cohort (2.1 or 3.1) – ≥2 DLT in renal cohort = maximum administered dose – dose escalation ends with that renal cohort
≥2 (marrow only)	– dose adjust to appropriate renal cohort (2.1 or 3.1) – ≥2 DLT in renal cohort = maximum administered dose – dose escalation ends with that renal cohort
≤1 out of 6	– highest level below maximumally administered – termed 'maximum tolerated dose' (MTD) – generally considered recommended phase 2 dose

Figure 1 Trial design Trial design for results presented herein.

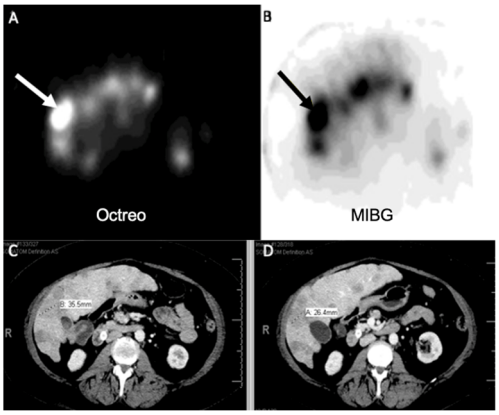


Figure 2 Subject #1 A. ^{111}In pentetreotide axial SPECT image through mid-liver demonstrating multiple octreopeptide positive metastases with focal intense uptake in a target lesion (white arrow). **B**. ^{131}I MIBG SPECT axial slice at same level demonstrating intense uptake in same lesion (black arrow). **C**. Corresponding baseline venous phase CT depicting multiple liver metastases consistent with SPECT findings. Target lesion 35.5 mm maximum diameter. D. 6-month post cycle 2 follow-up CT showing measurement on target lesion (maximum diameter 26.4 mm)

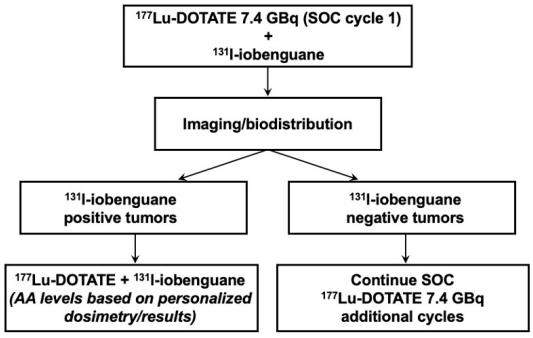


Figure 3 Modified Trial Design: (SOC=standard of care)

Tables

Table 1 Calculated administered activity levels to deliver 1900 cGy renal plus 150 cGy bone marrow				
	maximum total activity **^{90}Y DOTATOC only** (GBq)	In combination max total activity (^{90}Y **DOTATOC plus ^{131}I MIBG)**		
		^{90}Y DOTATOC (GBq)	^{131}I MIBG (GBq)	
Subject 1	10.8	8.7	11.4	
Subject 2	7.8	5.6	18.3	
Subject 3	5.0	2.8	18.7	

Table 2 Post treatment renal and bone marrow toxicity assessment						
	Baseline	**Cycle1: 1 month**	**Cycle1: 2 months**	**Cycle2: 1 month**	**Cycle2: 2 months**	**Cycle2: 6 months**
Creatinine (mg/dL)						
Subject 1	1.20	1.1	1.10	1.30	1.10	1.60
Subject 2	1.10	0.86	0.94	0.98	1.13	1.00
Subject 3	1.10	1.14	0.95	1.00	1.07	1.10
Platelet (k/mm^3)						
Subject 1	396	151	215	191	216	165
Subject 2	187	82	128	86	130	189
Subject 3	253	107	150	111	47	173
Absolute Neutrophil Count (cells/mm^3)						
Subject 1	5050	6510	4310	5630	4560	4100
Subject 2	6510	4500	3800	4100	4800	5180
Subject 3	3230	3393	1575	3281	1332	3520