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Efficacy of Peptide Receptor Radionuclide Therapy in a United States Based Cohort of Metastatic Neuroendocrine Tumor Patients: Single-Institution Retrospective Analysis

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Abstract

Objectives—Retrospective cohort study of a United States based-group of metastatic neuroendocrine tumor (NET) patients who underwent peptide receptor radionuclide therapy (PRRT).

Methods—Twenty-eight patients from a single United States NET Center were treated with PRRT. Toxicities were assessed using CTCAE v4.03. Progression was determined by RECIST 1.1. Univariate and multivariate Cox regression was performed to identify potential predictors of progression free survival (PFS) and overall survival (OS).

Results—The median age of NET diagnosis was 56 years, 50% of the patients were male, 46% of NET primaries were located in the pancreas, 71% of tumors were non-functional, 25% were WHO grade III, and 20% had at least a 25% hepatic tumor burden. Anemia (36%) was the most common post-PRRT toxicity, followed by leukopenia (31%), nephrotoxicity (27%), and thrombocytopenia (24%). Median PFS was 18 months, and median OS was 38 months. Having a WHO grade III NET or receiving systemic chemotherapy prior to PRRT were found to be independent predictors of shorter PFS and OS.

Conclusions—PRRT is an effective therapy in a United States population. PFS and OS were better in WHO grade I/II NETs and when PRRT was sequenced prior to systemic chemotherapy.

Introduction

Neuroendocrine tumors (NETs) represent a heterogeneous group of tumors that arise from neuroendocrine cells located in many different locations throughout the body. NETs were once thought to be very rare tumors, however their incidence has increased more than 5-fold in the last three decades.^{1,2} Moreover, NETs are often indolent, and it has been estimated that there are more than 120,000 individuals with metastatic NETs living in the United States.² As there are multiple different types of therapies available for NETs, the effective treatment of neuroendocrine tumors typically requires a multi-disciplinary team including oncologists, surgeons, gastroenterologists, and radiologists including those specializing in interventional radiology and nuclear medicine. Therefore, understanding the different

treatment options for these patients is becoming increasingly important for an ever-growing number of practitioners.

Peptide receptor radionuclide therapy (PRRT) exploits the somatostatin receptor positivity of the majority of NETs to allow selective delivery of toxic radionuclides conjugated to somatostatin analogs.³ The two most commonly utilized radionuclides are ⁹⁰Yttrium (⁹⁰Y) and ¹⁷⁷Lutetium (¹⁷⁷Lu), and PRRT has been shown to be effective in the treatment of NETs.^{4–12} The recent NETTER-1 trial compared patients with well-differentiated, metastatic, mid-gut neuroendocrine tumors who were treated with ¹⁷⁷Lu-Dotatate plus octreotide long-acting repeatable (LAR) versus octreotide LAR alone.¹³ Progression-free survival (PFS) at month 20 was 65.2% in the ¹⁷⁷Lu-Dotatate group compared to 10.8% in the octreotide LAR alone group, supporting the effectiveness of PRRT for the treatment of well-differentiated mid-gut NETs. Preliminary evidence also points to an increase in overall survival (OS) with PRRT, and a post hoc analysis demonstrated improved quality of life in those receiving PRRT (Strosberg J., et al., ENETS abstract 2017). Although PRRT is considered to be a well-tolerated treatment, there are risks associated with PRRT including myelosuppression, nephrotoxicity, and hepatotoxicity. We previously identified a higher than expected risk of hepatotoxicity in NET patients from the United States who underwent PRRT therapy, which we attributed to heavy liver pretreatment prior to the receipt of PRRT.¹⁴

While PRRT has been used regularly in Europe for many years with good outcomes in patients with a variety of primary tumor subtypes^{3,11}, the use of PRRT in the United States has been far less common given its current lack of U.S. Food and Drug Administration (FDA) approval and limited access in North America. A recent report in an exclusively North American population demonstrated that PRRT was associated with a median PFS of nearly 24 months and median OS of 40 months, demonstrating its efficacy in North American NET patients.¹⁵ However, what remains unclear is where PRRT fits into the already complicated treatment algorithm of metastatic NETs. This question will become increasingly important as FDA approval for PRRT in the United States is expected in the near future. To help answer this question, we analyzed the outcomes of our United States-based NET patients who underwent PRRT therapy.

MATERIALS AND METHODS

We conducted a retrospective cohort study on all patients seen in the University of Pennsylvania NET Clinic with metastatic NETs who underwent PRRT between 2005 and January of 2017 (N = 32). The study was approved by the University of Pennsylvania institutional review board. Patients receiving PRRT under a clinical trial (N = 4) were excluded from the analysis, leaving a final cohort of 28 patients. All subjects underwent PRRT in Europe, primarily in Basel, Switzerland. The electronic medical records of all patients in the cohort were manually reviewed to extract study-related data. The data collected included sex, date of birth, date of death (if applicable), date of NET diagnosis, primary tumor location, grade, functionality, and location of metastases. Information regarding PRRT included dates of treatment, as well as the isotopes and doses used. Additionally, information about the use of other therapies pre-PRRT were collected

including non-hepatic surgery, liver directed therapies including transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiofrequency ablation (RFA), bland embolization, and hepatic resection, and systemic chemotherapy which was defined as having systemic treatment for a malignancy with any non-somatostatin analog (SSA) agent. Laboratory data including white blood cell (WBC) count, hemoglobin (Hgb), platelets (Plt), creatinine (Cr), estimated glomerular filtration rate (eGFR), total bilirubin (Bili), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were also retrieved from the medical records.

Toxicities were determined based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria from the National Institutes of Health/National Cancer Institute, and were defined as the development of a new grade 2 or higher toxicity within 1 year of the start of PRRT.¹⁶ More specifically, for hematologic toxicities leukopenia, anemia, and thrombocytopenia were defined as the new development of a WBC less than 3000/mm³, Hgb less than 10g/dL, and Plt count less than 75,000/mm³ respectively, within 1 year of the start of PRRT. Nephrotoxicity was defined as the new development of an eGFR < 60mL/min/1.73m² within 1 year of the start of PRRT. Biochemical liver injury was defined as the new development of a Bili > 1.5 × the upper limit of normal, AST > 3 × the upper limit of normal, or ALT > 3 × the upper limit of normal within 1 year of the start of PRRT. Tumor progression was determined by comparison of pre- and post-PRRT imaging using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.¹⁷ There were 3 patients, who after undergoing their first treatment course of PRRT, developed progression and were retreated with additional courses of PRRT at a later date. Toxicities were calculated for each distinct PRRT treatment course independently. OS was calculated based on the first session of the first treatment course of PRRT. For statistical purposes, the time to progression after the first session of the first treatment course of PRRT was utilized in the analysis. However for patients undergoing PRRT retreatment, progression was determined after the first session of PRRT in each distinct PRRT treatment course, to allow for separate comparisons for the 3 patients who underwent repeated therapies.

Statistical Analyses

Median PFS and OS following the initiation of PRRT were determined using Kaplan-Meier estimates and differences between groups were examined with the log-rank test. Univariable Cox proportional hazards regression was performed to identify factors associated with PFS and OS, and data are presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). Multivariable models were adjusted for pertinent covariates that could impact the association between a variable of interest and PFS and OS following PRRT; these covariables included age at the initiation of PRRT, gender, primary NET location, WHO grade III histology, and prior systemic chemotherapy. The Wald test was used to test for an interaction between WHO grade III and pre-PRRT treatment modalities (i.e. liver-directed therapy, non-hepatic resection, and systemic chemotherapy) given that the benefit of a given treatment on PFS and OS may be impacted by histologic grade and tumor biology. Two-sided p values <0.05 were considered statistically significant. Analyses were performed using STATA statistical software, version 14.0 (StataCorp, College Station, Texas).

RESULTS

Cohort Characteristics

The median age of NET diagnosis for the entire cohort was 56 years (range 35–69 years) and 50% of the patients were male (Table 1). The most common site of primary tumor location was the pancreas (46%) followed by the small intestine (29%), lung (14%), unknown primary location (7%), and colon (4%). Seventy one percent of the patients had non-functional tumors, whereas 14% had carcinoid syndrome, 7% gastrinoma, and 4% each glucagonoma or insulinoma. There was a distribution of NET WHO tumor grades: 18% with grade I, 46% with grade II, 25% with grade III, and 11% with an unknown grade. The most common location for metastases was the liver occurring in 93% of patients, followed by lymph nodes (68%), bone (29%), lung (18%), and other sites (18%). The majority of the patients had a liver tumor burden of <25% (80%), while the remainder of the patients had a range of tumor involvement of the liver: 25–49% (12%), 50–74% (4%), and 75% (4%).

The median age of PRRT commencement was 62 years (range, 37–74 years) with a wide range of time between NET diagnosis and PRRT initiation of 0–25 years (median of 3 years) (Table 2). The average number of PRRT sessions per patient was 2.5. Only three patients had more than 1 distinct treatment course of PRRT, and there was an average of 2.2 PRRT sessions per treatment course. There was variation in the type of PRRT isotope utilized with 34% receiving ^{90}Y , 25% receiving ^{177}Lu , and 41% receiving a combination of ^{90}Y and ^{177}Lu . The average dose of ^{90}Y administered was 160mCi and the average dose of ^{177}Lu administered was 200mCi. Prior to PRRT administration, many of the patients had multiple other forms of treatment for their NETs. Before initiation of PRRT, all but one of the patients were on maintenance SSA therapy, 79% of the patients had undergone liver directed therapy, 79% had non-hepatic surgery, and 39% had received systemic chemotherapy. Of those patients who received systemic chemotherapy, the most commonly administered regimen was capecitabine/temozolomide, which was administered in 6 of the 11 patients who had systemic chemotherapy prior to PRRT. The mean number of types of therapy utilized (with liver directed therapy, non-hepatic surgery, or systemic chemotherapy each counting as a single therapy type) prior to PRRT was 2 (range, 0–3).

Toxicity

Ten patients (36%) developed new anemia after PRRT (Table 2). Two of these patients had grade 3 or higher anemia, both of whom developed long-term transfusion dependence. Eight patients (31%) developed new leukopenia, with three of these patients developing grade 3 or higher toxicity, and seven patients (24%) developed new thrombocytopenia, with five of these patients developing grade 3 or higher toxicity. No patients in our cohort developed myelodysplastic syndrome. Seven patients (27%) developed nephrotoxicity, with two of these patients developing grade 3 or higher toxicity, however none went on to require chronic hemodialysis. Four patients developed (14%) new biochemical liver injury as determined by having elevations of bilirubin, AST, or ALT, with three of these patients developing grade 3 or higher toxicity and two of these patients ultimately dying of liver failure within the first year after PRRT.

Progression Free Survival

The median duration of follow up for progression free survival (PFS) for the 28 patients was 12 months (range, 1–53 months). Eighteen patients (64%) experienced disease progression during follow up. Median PFS was 18 months (interquartile range [IQR], 6–25 months) (Figure 1A). The results of univariable Cox proportional hazards regression for PFS are shown in Table 3. Disease progression was associated with WHO grade III histology (vs. WHO grade I or II, unadjusted hazard ratio [HR], 3.41; 95% CI, 1.13–10.30). This association remained statistically significant after adjusting for patient age, gender and primary tumor location (HR, 3.71; 95% CI, 1.01–13.73). Median PFS was 20 months and 5 months for WHO grade I/II and WHO grade III respectively (Figure 1B). Systemic chemotherapy prior to PRRT was associated with an increased risk of disease progression after PRRT (HR, 4.76; 95% CI, 1.64–13.77) that remained significant after adjusting for patient age, gender, WHO grade III, and primary tumor location (HR, 3.66; 95% CI, 1.15–11.64). Median PFS was 7 months in patients who had previously received chemotherapy prior to PRRT versus 25 months in patient who did not (Figure 1C). There was a trend towards improved PFS in patients who had previously received liver-directed therapy (HR, 0.45; 95% CI, 0.16–1.28). This association was most pronounced in patients with WHO grade III histology (HR, 0.12; 95% CI, 0.01–1.24), suggesting an effect modification of the association between liver directed therapy and PFS by WHO grade (Wald test *P* value for interaction term = 0.06). Gender, primary NET location in either the pancreas or small bowel, age greater than 60 at the time of PRRT, number of different pre-PRRT treatment modalities, having non-hepatic surgery prior to PRRT, and hepatic tumor burden involving 25% of the liver parenchyma were not associated with a statistically significant differences in PFS.

Overall Survival

The median duration of follow up for overall survival (OS) for the 28 patients was 18 months (range 3–141 months). Twelve patients (43%) died following PRRT with a median OS of 38 months (Figure 1D). The results of univariable Cox proportional hazards regression for OS are shown in Table 3. In an unadjusted analysis, WHO grade III was significantly associated with death (HR, 3.61; 95% CI, 1.04–12.60). Median OS for patients with WHO grade III was 18 months (Figure 1E). Fewer than 50% of the patients with WHO grade I or II died during the follow-up period. Following adjustment for age, gender, and NET primary location, only a statistically non-significant trend towards increased risk of death remained in patients with WHO grade III histology (HR, 4.02; 95% CI, 0.81–20.00). Prior systemic chemotherapy was associated with an increased risk of death (HR, 3.53; 95% CI, 1.08–11.55), which remained significant after adjusting for age, gender, NET primary location, and WHO grade III (HR, 4.93; 95% CI, 1.06–22.97). Median OS was significantly lower in patients having received prior systemic chemotherapy (18 vs. 42 months) (Figure 1F). Gender, primary NET location in either the pancreas or small bowel, age greater than 60 at the time of PRRT, number of different pre-PRRT treatment modalities, hepatic tumor burden involving 25% of the liver parenchyma, and having non-hepatic surgery or liver directed therapy prior to PRRT were not associated with the risk of death.

Retreatment With PRRT

There were three patients in our cohort who after their initial course of PRRT, were retreated with additional PRRT after tumor progression. Two patients had 2 distinct PRRT treatment courses, while one patient had 3 distinct PRRT treatment courses. All three of these retreated patients showed some response after each individual PRRT course, however comparison of PFS demonstrated that PFS decreased with each subsequent treatment course (Figure 2).

DISCUSSION

With future FDA approval of PRRT on the horizon, PRRT will soon become a more commonly utilized therapy for the treatment of metastatic NETs in the United States. Adding a new therapy into the plethora of treatment modalities for metastatic NETs that are already available will pose challenges for treatment teams, especially when trying to decide where PRRT should be utilized in the treatment algorithm. Therefore, in this study we attempted to characterize the PRRT response in a cohort of metastatic NET patients from our tertiary center in the United States.

As NETs constitute a very heterogeneous groups of tumors, our patient cohort was also extremely heterogeneous, including an equal distribution of gender, wide range of ages, multiple sites of primary tumor location, and a wide variety of WHO grades. As for the PRRT treatment, the patients treated in our cohort had a mixture of isotopes utilized during therapy including ^{90}Y alone, ^{177}Lu alone, and also a combination of ^{90}Y and ^{177}Lu . The toxicity of PRRT has been previously reported on extensively in the literature,^{18–23} including by our group,¹⁴ however this current report updates our toxicity experience for our entire cohort within the first year after starting PRRT. Portions of our cohort experienced transient toxicity in the form of anemia, leukopenia, thrombocytopenia, nephrotoxicity, and biochemical liver injury after PRRT therapy. Anemia was the most common toxicity seen, however the anemia, as with most of the toxicities observed, was typically transient as only 2 patients went on to develop transfusion dependence. Rates of biochemical liver injury were low in our completed analysis, however 3 patients (11%) died from liver related complications early on in our experience. This is a novel observation in comparison with other reports in the literature, which we believe relates to the extent of disease and heavy liver pretreatment of our patients prior to receiving PRRT.

Using RECIST 1.1 criteria to assess progression on imaging, we found that our cohort's median PFS was 18 months while the median OS was 38 months. These results are similar to another recent report of PRRT in a United States NET population.¹⁵ However, the median PFS from our study is lower than that reported in the recent NETTER-1 study.¹³ One factor that could contribute to this difference is the inclusion of WHO grade III NETs in our analysis. While all of the grade III NETs that were treated with PRRT from our center were somatostatin receptor positive, our data demonstrate that grade III NETs had a worse PFS and OS compared to grade I/II NETs, which is not unexpected given the natural history and biology of low grade versus high grade NETs. In our cohort, gender, primary location (in either the pancreas or small bowel), or age greater than 60 years were not associated with any significant change in PFS or OS, which is in agreement with other studies in Europe.¹¹

As NETs are typically treated in a sequential fashion with a variety of different therapies, it is important to try to understand where in the treatment course PRRT should be utilized, especially as the data is limited regarding the best order of treatment. This question of where PRRT should be utilized continues to be a subject of debate in recent society guidelines addressing the treatment of pancreatic and midgut neuroendocrine tumors.^{24,25} In our cohort we analyzed PFS and OS in patients who were treated with either non-hepatic surgery, liver directed therapy including hepatic resection, and/or systemic chemotherapy prior to PRRT. The total number of different treatments and having a non-hepatic surgery prior to PRRT did not affect PFS or OS in our analysis. Of interest, there was a trend toward improved PFS in patients who received liver-directed therapy prior to PRRT, especially for those with WHO grade III tumors, however this trend did not meet statistical significance and these results may be subject to a selection bias as patients who underwent liver-directed therapy prior to PRRT may have had more limited disease to start with. Nevertheless, larger studies would be useful to determine if in fact liver directed therapy prior to PRRT may potentially enhance the efficacy of PRRT. An additional interesting point from our analysis was that patients who received systemic chemotherapy at any point prior to PRRT had a significantly worse PFS and OS compared to those who did not receive chemotherapy prior to PRRT. These results also remained statistically significant after adjusting for age, gender, WHO grade, and primary NET location. The decreased PFS and OS after PRRT in patients receiving prior chemotherapy has interesting implications regarding the position of PRRT in the treatment algorithm of NETs by suggesting that PRRT may be more effective if utilized earlier in the treatment algorithm prior to systemic chemotherapy. However, to properly study this effect would require prospective studies in larger cohorts, and if validated in larger studies the biology of this effect would also necessitate further investigation as certain chemotherapeutic agents may induce cellular changes that promote resistance to PRRT.

Finally, we had three patients in our cohort who underwent retreatment with PRRT after tumor progression, and therefore received multiple distinct PRRT treatment courses. Prior studies have demonstrated that this treatment strategy is safe from a toxicity perspective.^{26–29} Our data demonstrates that with each successive course of PRRT, although the patients responded to therapy, the PFS decreased. Given the small number of patients who underwent retreatment as well as the retrospective nature of this study, we cannot draw firm conclusions from this data, however it is important to highlight that our NET patients who underwent retreatment with PRRT did show response to each successive treatment course.

Our study has limitations, including the small sample size and heterogeneity of the cohort. However, given that there are few published data on the outcomes of United States-based cohorts of NET patients undergoing PRRT, and that this therapy will presumably become available within the next year, we believe that it is important to report these results despite the size limitation. Additionally, our study is retrospective in nature and was performed at a tertiary medical center which allows for selection bias in the patients. Another selection bias arises given that the PRRT treatment was performed in Europe, which required that patients had the ability and means to make the trip overseas for their treatment.

In summary, PRRT is increasingly becoming recognized as a cornerstone of the treatment of metastatic NETs and will soon be more widely available for the treatment of NET patients in the United States. Our data suggest that PRRT is effective for the treatment of metastatic NETs in United States patients. Furthermore, we show that PFS and OS are better in grade I/II NETs and when PRRT is used earlier in the treatment course prior to the use of systemic chemotherapy. Larger prospective studies will need to be performed after FDA-approval of PPRT to better understand how this important therapy can be utilized most effectively for the treatment of metastatic NETs.

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FIGURE 1. Kaplan-Meier plots of progression free survival (PFS) and overall survival (OS) after PRRT treatment

A, PFS for the entire cohort. B, PFS comparison between WHO Grade I/II NETs and WHO Grade III NETs. C, PFS comparison between patients who had and did not have systemic chemotherapy prior to PRRT. D, OS for the entire cohort. E, OS comparison between WHO Grade I/II NETs and WHO Grade III NETs. F, OS comparison between patients who had and did not have systemic chemotherapy prior to PRRT.

FIGURE 2. Progression free survival (PFS) after retreatment with PRRT

Three patients in the cohort underwent retreatment with PRRT. PFS is plotted for each distinct PRRT treatment course.

TABLE 1**Metastatic NET Patient Characteristics (N = 28)**

Age of diagnosis, median (range), y	56 (35–69)
Sex, %	
Female	50
Male	50
Primary NET Location, %	
Pancreas	46
Small intestine	29
Lung	14
Unknown	7
Colon	4
NET Functionality, %	
Non-functional	71
Carcinoid syndrome	14
Gastrinoma	7
Glucagonoma	4
Insulinoma	4
NET Grade, %	
Grade I	18
Grade II	46
Grade III	25
Unknown	11
Metastasis location at the start of PRRT, %	
Liver	93
Lymph nodes	68
Bone	29
Lung	18
Other	18
Liver tumor burden, %	
<25%	80
25% – 49%	12
50% – 74%	4
75%	4

TABLE 2

PRRT Treatment Characteristics and Toxicities

Age at the start of PRRT, median (range), y	62 (37–74)
Years between NET diagnosis and initiation of PRRT, median (range), y	3 (0–25)
PRRT sessions per patient, mean (range)	2.5 (1–7)
Sessions per course of PRRT treatment, mean (range)	2.2 (1–3)
Type of PRRT isotope, %	
⁹⁰ Y	34
¹⁷⁷ Lu	25
⁹⁰ Y and ¹⁷⁷ Lu	41
Dose of PRRT given per session, median (range), mCi	
⁹⁰ Y	160 (120–200)
¹⁷⁷ Lu	200 (100–200)
Therapies administered prior to initiating PRRT, %	
Somatostatin analog therapy	96
Liver directed therapy	79
Non-hepatic surgery	79
Systemic chemotherapy	39
Number of different therapies prior to first PRRT, mean (range)	2 (0–3)
Toxicities that developed during the first year after starting PRRT, %	
Anemia	36
Leukopenia	31
Thrombocytopenia	24
Nephrotoxicity	27
Biochemical liver injury (any)	14
Hyperbilirubinemia	8
Elevated AST	12
Elevated ALT	7

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase

TABLE 3
Progression Free survival (PFS) and Overall Survival (OS) After Treatment With PRRT

Variable	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
Sex, male	1.23	0.46–3.30	0.68	0.86	0.27–2.73	0.80
Pancreatic primary	0.85	0.33–2.17	0.73	1.37	0.44–4.26	0.59
Small bowel primary	1.29	0.45–3.69	0.63	0.64	0.14–2.93	0.56
WHO grade III	3.41	1.13–10.30	0.03	3.61	1.04–12.60	0.04
Age >60 years at start of PRRT	0.50	0.19–1.32	0.16	1.08	0.34–3.43	0.90
Total treatments prior to PRRT	1.24	0.62–2.47	0.60	1.19	0.52–2.74	0.68
Non-hepatic surgery	0.78	0.22–2.76	0.71	0.62	0.13–2.90	0.55
Liver directed therapy	0.45	0.16–1.28	0.13	0.50	0.13–1.89	0.31
Chemotherapy	4.76	1.64–13.77	<0.01	3.53	1.08–11.55	0.04
Hepatic tumor burden (> 25%)	2.49	0.76–8.19	0.13	1.42	0.37–5.39	0.61

Bolded values are statistically significant with a $P < 0.05$.