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Peptide Receptor Radionuclide Therapy of Late-stage Neuroendocrine Tumor Patients with Multiple Cycles of ^{177}Lu-DOTA-EB-TATE

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Running title: ^{177}Lu-DOTA-EB-TATE therapy in NET

ABSTRACT

Purpose: This study aimed to evaluate the safety and efficacy of multiple cycles of ^{177}Lu-DOTA-EB-TATE peptide receptor radionuclide therapy (PRRT) at escalating doses in neuroendocrine tumors (NETs).

Methods: A total of 32 NET patients were randomly divided into 3 groups and treated with escalating doses: group A (1.17 ± 0.09 GBq/cycle); group B (1.89 ± 0.53 GBq/cycle); group C (3.97 ± 0.84 GBq/cycle). The treatment was planned up to three cycles. Treatment-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v.5.0). Treatment response was referred to European Organization for Research and Treatment of Cancer criteria (EORTC) and modified positron emission tomography response criteria in solid tumors (PERCIST) criteria.

Results: Administration of PRRT was well tolerated without life-threatening (CTC-4) AEs. CTC-3 hematotoxicity was recorded in 1 patient (16.6%) in group B (thrombocytopenia) and 3 patients (21.4%) in group C (thrombocytopenia in 3, anemia in 1). CTC-3 hepatotoxicity was recorded in 1 patient in group A (8.3%) and C (7.1%), respectively with elevated AST. No nephrotoxicity was observed. When referring to EORTC criteria, the overall disease response rates (DRR) were similar in groups A-C (50.0%, 50.0%, and 42.9%, respectively), and the overall disease control rates (DCR) were higher in group B (83.3%) and C (71.5%) than that in group A (66.7%). When referring to modified PERCIST criteria, lower DRR but similar DCR was found. When selecting comparable baseline SUVmax ranging from 15 to 40, the ΔSUVmax% had slight increase in group A (ΔSUVmax% = 2.1 ± 40.8) but significant decrease in groups B and C (ΔSUVmax% = -38.7 ± 10.0 and -14.7 ± 20.0) after the 1st PRRT (P =0.001),

and had decrease in all three groups after the 3rd PRRT (groups A-C, ΔSUVmax%= -6.9 ± 42.3, -49.2 ± 30.9, -11.9 ± 37.9, P = 0.044).

Conclusions: Escalated doses of ^{177}Lu-DOTA-EB-TATE up to 3.97 GBq/cycle seem to be well tolerated. 1.89 GBq/cycle and 3.97 GBq/cycle ^{177}Lu-DOTA-EB-TATE were both effective in tumor control and more effective than 1.17 GBq/cycle ^{177}Lu-DOTA-EB-TATE.

Key Words: ^{177}Lu-DOTA-EB-TATE; neuroendocrine tumor; dose escalation; peptide receptor radionuclide therapy (PRRT)

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originated from the diffuse neuroendocrine system. Data of Surveillance, Epidemiology, and End Results program registries showed the incidence rate of NETs increased by 6.4-fold from 1973 to 2012 (*1*). However, due to the rarity, tumor heterogeneity, non-specific clinical behaviors and slow growth, the diagnosis of NETs can be delayed even up to 7 years (*2,3*). Thus, at the time of diagnosis, over 50% of NET patients are at an advanced stage when surgery is no longer advised (*4*).

NETs are characterized with abundant expression of somatostatin receptor 2, providing important target for peptide receptor radionuclide therapy (PRRT). ^{177}Lu-DOTA-TATE is the most commonly used radiopharmaceutical for PRRT. Although ^{177}Lu-DOTA-TATE has been approved in Europe and USA for the treatment of NETs, optimization is still ongoing to further improve the therapeutic efficacy. Evans blue (EB) dye has reversible binding to serum albumin (*5,6*), which is an excellent candidate carrier to prolong the half-life of rapidly clearing ^{177}Lu-DOTA-TATE.

^{177}Lu-DOTA-EB-TATE was developed based on ^{177}Lu-DOTA-TATE, modified with EB to have a much longer circulation half-life (*7,8*). Preclinical studies showed that compared with the similar radioactive dose of ^{177}Lu-DOTA-TATE, ^{177}Lu-DOTA-EB-TATE had approximately 4-fold higher tumor dose and more effective tumor control (*7,9*). Applying ^{177}Lu-DOTA-EB-TATE in humans also showed about 8-fold higher tumor dose, but also 3.2-fold higher in kidneys and 18.2-fold higher in bone marrow than ^{177}Lu-DOTA-TATE (*10*). The results were encouraging even after one cycle of PRRT in NET patients (*11*). In this study, we aim to further evaluate the

safety and efficacy of multiple cycles of ^{177}Lu-DOTA-EB-TATE with escalating doses in the treatment of NETs.

MATERIALS AND METHODS

Patients

This study was registered at the Clinicaltrials.gov (NCT03478358) and approved by the Institute Review Board of Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences and PUMC. From August 2017 to June 2019, 32 patients with histologically confirmed NET were recruited in this prospective study. All subjects signed a written informed consent. The inclusion criteria were the same as described in our previously published study (*11*).

Patients were randomly divided into 3 groups (groups A-C) using sequentially numbered, opaque sealed envelopes method. Group A (n = 12, male/female = 7/5, mean age 53 ± 13 y) were treated with 1.17 ± 0.09 GBq/cycle (31.6 ± 2.4 mCi/cycle) of ^{177}Lu-DOTA-EB-TATE; group B (n = 6, male/female = 4/2, mean age 55 ± 10 y) were treated with 1.89 ± 1.53 GBq/cycle (51.1 ± 14.3 mCi/cycle) of ^{177}Lu-DOTA-EB-TATE; group C (n = 14, male/female = 7/7, mean age 50 ± 10 y) were treated with 3.97 ± 0.84 GBq/cycle (107.3 ± 22.7 mCi/cycle) of ^{177}Lu-DOTA-EB-TATE. A participant flow chart of the 3 randomized groups was shown in **Fig. 1**.

Treatment Regimen and Follow Up

Preparation of DOTA-EB-TATE and ^{177}Lu labeling were performed as described previously (*11,12*). The treatments were planned up to three cycles and repeated at 8-12 weeks intervals.

Hematological parameters, liver and renal function were tested at baseline, 1 week and 4 weeks after each cycle of treatments. ^{68}Ga-DOTATATE PET/CT were performed at baseline, some days before the 2nd-3rd cycle and 2–3 months after the last cycle of treatment.

Safety and Symptom Evaluation

Treatment-related adverse events (AEs) were recorded over a period of 8-12 weeks after the administration of PRRT. Hematoxicity, hepatotoxicity and nephrotoxicity were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0).

Functional performance was assessed by Eastern Cooperative of Oncology Group (ECOG) at baseline and 8-12 weeks after last cycle of PRRT.

^{68}Ga-DOTATATE PET/CT Response Evaluation

The molecular imaging ^{68}Ga-DOTATATE PET/CT response was evaluated in reference to European Organization for Research and Treatment of Cancer criteria (EORTC) and modified positron emission tomography response criteria in solid tumors (PERCIST) criteria. Images were evaluated by the same physician who was masked to the clinical data.

Statistical Analysis

The change percentage of tumor SUVmax (ΔSUVmax%) was obtained by dividing the ΔSUVmax by baseline SUVmax. Data were analyzed using SPSS 23.0 software (IBM SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant. Quantitative data were expressed as means ± standard deviations. Statistics among groups were conducted by using one-way analysis of variance or nonparametric test.

RESULTS

Patients

The median cycles of PRRT groups A-C were 3. In group A, the median cumulative administered activity was 3.5 GBq (range 2.2-3.7 GBq). All 12 patients received the 1st and 2nd cycle of PRRT, 9 (75.0%) patients received the 3rd cycle of PRRT. In group B, the median cumulative administered activity was 5.7 GBq (range 1.9-6.0 GBq). All the 6 patients received the 1st cycle of PRRT, 5 (83.3%) patients received the 2nd and 3rd cycle of PRRT. In group C, the median cumulative administered activity was 10.5 GBq (range 4.1-14.3 GBq). All 14 patients received the 1st cycle of PRRT, 13 (92.3%) patients received the 2nd cycle of PRRT and 8 (57.1%) patients received the 3rd cycle of PRRT. Details of baseline characteristics were listed in **Table 1** and no significant difference was observed among groups.

Safety Evaluation

Generally, patients tolerated PRRT well with no immediate adverse effects such as irritating pain, allergy or fever during administration and no life-threatening AEs (CTC-4) during the observation period. Only 1 patient in group C had tolerable nausea and vomiting several hours after administration but recovered within 2 weeks in every cycle of PRRT. All the scheduled laboratory tests were obtained.

Hematotoxicity

No life-threatening CTC-4 hematotoxicity was observed in groups A-C. In group A, no CTC-3 hematotoxicity was reported. In group B, CTC-3 hematotoxicity (thrombocytopenia) was recorded in 1 patient (16.6%) who was diagnosed with grade 2 myelosuppression 2 years ago due to previous radiotherapy. In group C, 3 (21.4%) patients had CTC-3 hematotoxicity (thrombocytopenia in 3 patients, anemia in 1 patient). Among these 3 patients, PLT counts, which are reported preferentially being affected after 3rd cycle of ^{177}Lu-PRRT (*13*), dropped greatly after the 1st cycle of PRRT. All 3 patients had prior exposure to multi-courses of alkylating therapy or sulfatinib/everolimus, which were very important predisposing factors of hematotoxicity (*14*) (**Supplemental Table S1**).

The changes of WBC, Hb and PLT between baseline and 4 weeks after each cycle of treatment were listed in **Supplemental Table S2** for comparison. Significant difference in ΔHb% among groups A-C was observed in the 2nd and 3rd cycles of PRRT ($P < 0.001$ and $P =$

0.015, respectively) with Hb significantly increased in group A (2nd: ΔHb% = 1.8 ± 9.2, P < 0.001; 3rd: ΔHb% = 7.1 ± 12.6, P = 0.004) and group B (2nd: ΔHb% = 5.3 ± 10.8, P = 0.001; 3rd: ΔHb% = 1.1 ± 11.1, P = 0.011) when compared with group C (2nd: ΔHb% = -14.1 ± 7.8; 3rd: ΔHb% = -17.2 ± 14.4). No significant change was observed in WBC or PLT.

The mean counts of WBC, PLT and Hb at baseline, 1 week and 4 weeks after 1st to 3rd cycle of PRRT were shown in **Fig. 2A**. Generally, the mean counts of WBC, PLT and Hb fluctuated within the normal ranges and were consistent in all patients and patients who received 3 cycles of PRRT. PLT was mainly affected, followed by WBC and Hb, occurring predominantly after the 2nd PRRT. WBC and PLT were relatively stable in groups A-C. Whereas for Hb, it dropped the most in group C as compared to groups A and B.

Hepatotoxicity

No life-threatening CTC-4 hepatotoxicity was observed in groups A-C. CTC-3 hepatotoxicity was only recorded in 1 patient in group A (8.3%) and C (7.1%), respectively with elevated AST. Disease-related liver dysfunction could not be excluded in group A. The patient had liver dysfunction of unknown cause 6 months before PRRT and 3 months later after cessation of the last cycle of PRRT. As for the patient in group C with normal baseline liver function, he had transient simultaneous rises in serum ALT, AST and bilirubin but recovered before the 2nd cycle of PRRT. This is probably a transient reaction caused by edema and necrosis of tumors squeezing the normal liver tissue, rather than radiotoxicity (**Supplemental Table S1**).

No significant change of ALT and AST between baseline and 4 weeks after each cycle of treatment was observed in groups A-C (**Supplemental Table S2**). The mean counts of ALT and AST at baseline, 1 week and 4 weeks after 1st to 3rd cycle of PRRT were shown in **Fig. 2B** (upper and lower, respectively). Within the reference ranges, ALT and AST fluctuated the most and generally elevated in group C, while generally decreased in groups A and B.

Nephrotoxicity

No CTC-2/3/4 nephrotoxicity was observed (**Supplemental Table S1**). Significant difference in ΔCr% among groups A-C was observed in the 1st and 2nd cycle of PRRT (P = 0.040, P = 0.033) with decreased Cr in group B (1st: ΔCr% = -6.6 ± 16.7, P = 0.035; 2nd: ΔCr% = -10.2 ± 16.6, P = 0.016) and group C (1st: ΔCr% = -6.4 ± 19.0, P = 0.010; 2nd: ΔCr% = -6.3 ± 11.0, P = 0.011) when compared with increased creatine in group A (1st: ΔCr% = 13.8 ± 21.0; 2nd: ΔCr% = 11.5 ± 18.6) (**Supplemental Table S2**).

Response Evaluation

Functional Performance Evaluation

Except for 2 patients in group C who went from ECOG 2 to ECOG 3, ECOG scores of the other patients remained stable after therapy.

^{68}Ga-DOTA-TATE PET/CT Response

One patient in group C died after the 2nd PRRT due to progressive disease. Referring to EORTC criteria, the overall disease response rate (DRR) was similar in groups A-C (50.0%, 50.0%, and 42.9%, respectively). The overall disease control rate (DCR) were higher in group B (83.3%) and C (71.5%) than those in group A (66.7%). When referring to modified PERCIST criteria, lower DRR but similar DCR was found. Details were shown in **Supplemental Table S3**. Examples of treatment efficacy (PR) on ^{68}Ga-DOTATATE PET/CT were shown in **Fig 3**.

For all the selected qualified lesions, the ΔSUVmax% had significant difference among groups A-C (P = 0.044) after the 3rd PRRT, with significant decrease in groups B and C (ΔSUVmax% = -37.7 ± 34.2, -7.6 ± 65.8, respectively), but increase in group A (ΔSUVmax% = 8.1 ± 53.3) (Not shown).

For the lesions with comparable baseline SUVmax ranging from 15 to 40, the ΔSUVmax% had increase in group A (ΔSUVmax% = 2.1 ± 40.8) but significant decrease in group B and C (ΔSUVmax% = -38.7 ± 10.0 and -14.7 ± 20.0) after the 1st PRRT (P = 0.001). After the 3rd PRRT, the ΔSUVmax% had decrease in all three groups (groups A-C, ΔSUVmax% = -6.9 ± 42.3, -49.2 ± 30.9, -11.9 ± 37.9) (P = 0.044) (**Supplemental Table S4**). Similar results were also observed in patients who received 3 cycles of PRRT (**Supplemental Table S5**).

Groups B and C had significantly decreased SUVmax after 1st to 3rd PRRT when compared with baseline tumor SUVmax in patients who received 3 cycles of PRRT (P < 0.05). However,

no significant decrease was observed in group A ($P > 0.05$), indicating a poor tumor control than groups B and C (**Supplemental Table S6**).

DISCUSSION

Bone marrow (BM) is one of the dose-limiting organs in PRRT. Based on 2 Gy dose limit, the highest feasible dose of ^{177}Lu-DOTA-EB-TATE would be 34.3 GBq (radiation exposure of ^{177}Lu-DOTA-EB-TATE: 0.0582 ± 0.0137 mSv/MBq (*10*)). However, the validity of 2 Gy limit for ^{177}Lu-PRRT was questioned. Bergsma *et al.* (*15*) found that patients receiving four cycles of 7.4 GBq would already reach the 2 Gy dose limit. However, salvage PRRT, defined as re-challenge with one or more ^{177}Lu-DOTA-TATE therapy cycles after 4 initial PRRT cycles did not increase the risk of hematotoxicity (*16-18*). Therefore, the maximal dose of ^{177}Lu-DOTA-EB-TATE based on bone marrow tolerance might be more than 34.3 GBq.

Hematotoxicity is one of the concerning AEs in PRRT. In this study, CTC-3 thrombocytopenia was observed in 1 (16.6%) patient in group B, who was diagnosed with grade 2 myelosuppression previously. In group C, 3 (21.4%) patients had CTC-3 thrombocytopenia. Notably, PLT counts were reported to be preferentially affected after 3 cycles of ^{177}Lu-PRRT (*13*). However, in this study, PLT counts dropped greatly after the 1st cycle of PRRT in these 3 CTC-3 thrombocytopenia patients. Their prior exposure to multi-courses of alkylating therapy and sulfatinib/everolimus were important predisposing factors of hematotoxicity (*14*). The CTC-3/4 hematotoxicity rate of ^{177}Lu-DOTA-TATE/TOC was reported to be in the range of 3.1–12.5% (*13,15,16,19-24*), which was similar to what we observed in group B. While in a study

performed by Brieau *et al.* (*25*), the CTC-3/4 hematotoxicity rate was 30% (thrombocytopenia, neutropenia, and anemia in 25%, 15%, and 10%, respectively) among 20 patients who had received prior multicycles of chemotherapy. In this study, the majority of patients also had received several therapies prior to PRRT including chemotherapy, due to the unavailable PRRT in China previously. ^{177}Lu-PRRT commonly introduces thrombocytopenia, anemia and neutropenia (*14*), but no CTC-3/4 neutropenia or anemia was observed in this study, except for one of the 3 CTC-3 thrombocytopenia patients, who also had grade 3 anemia at baseline, but remained stable after PRRT. Thus, 3.97 GBq/cycle of ^{177}Lu-DOTA-EB-TATE may not develop higher risk of hematotoxicity as long as we take into consideration the importance of risk factors.

What's more, patients with extensive bone marrow involvement may tolerate ^{177}Lu-DOTA-EB-TATE well. In this study, one patient with extensive bone marrow metastasis in group A (Fig. 3A) had relatively good bone marrow function at baseline (normal WBC and PLT, but grade 2 anemia) after the treatment of surgery, sandostatin LAR, mTOR inhibitor (everolimus). However, no leukopenia or thrombocytopenia was observed after receiving 3 cycles of PRRT. In addition, Hb level remained stable after the 1st-PRRT, improved after the 2nd- (grade 1 anemia) and 3rd-PRRT (grade 0 anemia). Similar finding was found in other studies (*26,27*).

The maximum tolerated dose to kidneys for PRRT was reported in the range of 23-29 Gy (*28-30*). In order not to exceed absorbed dose of 23 Gy, the highest feasible dose of ^{177}Lu-DOTA-EB-TATE would be 20.0 GBq (radiation exposure of ^{177}Lu-DOTA-EB-TATE: 1.15 ± 0.92 mSv/MBq) (*10*). However, this limiting dose to the kidneys may not be directly translated

to PRRT with radiolabeled long-acting somatostatin analog ^{177}Lu-DOTA-EB-TATE, since it is characterized by a sustained but lower radiation dose rate, which is different from ^{177}Lu-DOTA-TATE. Therefore, the maximal dose of ^{177}Lu-DOTA-EB-TATE based on kidney tolerance might be more than 20 GBq. In this study, no CTCAE grade 2-4 nephrotoxicity was observed during any cycle of ^{177}Lu-DOTA-EB-TATE or on follow-up. This suggests that ^{177}Lu-DOTA-EB-TATE is very well tolerated without any nephrotoxicity during multiple cycles of PRRT with cumulative radioactivity up to 11 GBq.

A recent meta-analysis demonstrated the pooled DRR and DCR were approximately 25.0-42.0% and 75.0-83.0%, respectively, based on response evaluation criteria in solid tumors (RECIST) or southwest oncology group (SWOG) criteria (*31*). Similar results were shown in the other two meta-analyses (*32,33*). In this study, the DRRs in groups A-C were 50.0%, 50.0%, and 42.9%, respectively, the DCRs were 66.7%, 83.3%, and 71.5%, respectively. It seems to be equally effective as standard PRRT with 5.55-7.4 GBq/cycle, even with 1.17 GBq/cycle. Although a pooled study showed poor agreement of tumor responses between RECIST and EORTC criteria (*34*), Aras *et al.* (*35*) found a significant agreement among WHO (SWOG), RECIST, EORTC and PERCIST criteria. For early therapeutic response assessment in solid tumors, EORTC criteria appear to be more sensitive and accurate than RECIST (*36*).

In this study, 1.89 GBq/cycle of ^{177}Lu-DOTA-EB-TATE had almost no side effect and had better tumor response than 1.17 GBq/dose. However, 3.97 GBq/cycle of ^{177}Lu-DOTA-EB-TATE was still considered safe, except for patients who had prior exposure to chemotherapy with

alkylating agents. Furthermore, in this study, significant increase in Hb was observed in the 2nd and 3rd PRRT in groups A and B, but decrease in group C. Correspondingly, the DCR in group C was 92.9% after the 1st cycle, but dropped sharply to 69.3% and 62.5% after the 2nd and 3rd cycles. So far, we don't know reason for the sharp decline in therapeutic effect during the 2nd and 3rd PRRT in group C. Some literatures suggested that low Hb concentration may be one of the factors (*37,38*). Thus, with careful patient selection and adequate monitoring, 3.97 GBq or higher dose of ^{177}Lu-DOTA-EB-TATE is expected to achieve a better tumor response. Predicted blood biomarkers such as PRRT Predictive Quotient (PPQ) and NETest, probably would be helpful in predicting efficacy and monitoring disease (*39*).

There are several limitations in this study. First of all, the number of patients in each group is limited and uneven. Secondly, the analysis of overall survival and long-term toxicity is absent and will be conducted in the future. Finally, only three escalation doses were performed, and the maximum tolerated dose has not been determined. Further study with more patients and more escalation doses are warranted.

CONCLUSION

NET patients tolerated ^{177}Lu-DOTA-EB-TATE well with acceptable hematotoxicity. 1.89 GBq/cycle of ^{177}Lu-DOTA-EB-TATE appears to have good tumor response with almost no side effect. However, with careful patient selection and adequate monitoring, 3.97 GBq or a higher dose of ^{177}Lu-DOTA-EB-TATE may be still safe and expected a better tumor response.

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DISCLOSURE

No potential conflicts of interest relevant to this article exist.

KEY POINTS:

Question: Is multiple cycles of ^{177}Lu-DOTA-EB-TATE with escalating dose safe and effective in the treatments of advanced NETs? What's the optimal dose?

Pertinent Findings: In this prospective pilot study, a total of 32 NET patients were randomly divided into three escalating dose groups. Patients with NET seem to tolerate ^{177}Lu-DOTA-EB-TATE well, even up to 3.97 GBq/cycle. The overall disease control rate (DCR), as well as tumor SUVmax decrease (ΔSUVmax%), were the highest in 1.89 GBq/cycle ^{177}Lu-DOTA-EB-TATE, followed by 3.97 GBq/cycle and 1.17 GBq/cycle ^{177}Lu-DOTA-EB-TATE.

Implications For Patient Care: 1.89 GBq/cycle ^{177}Lu-DOTA-EB-TATE appears to have optimal tumor response with almost no side effect. With careful patient selection and monitoring, 3.97 GBq or higher dose of ^{177}Lu-DOTA-EB-TATE is expected to achieve a better tumor response.

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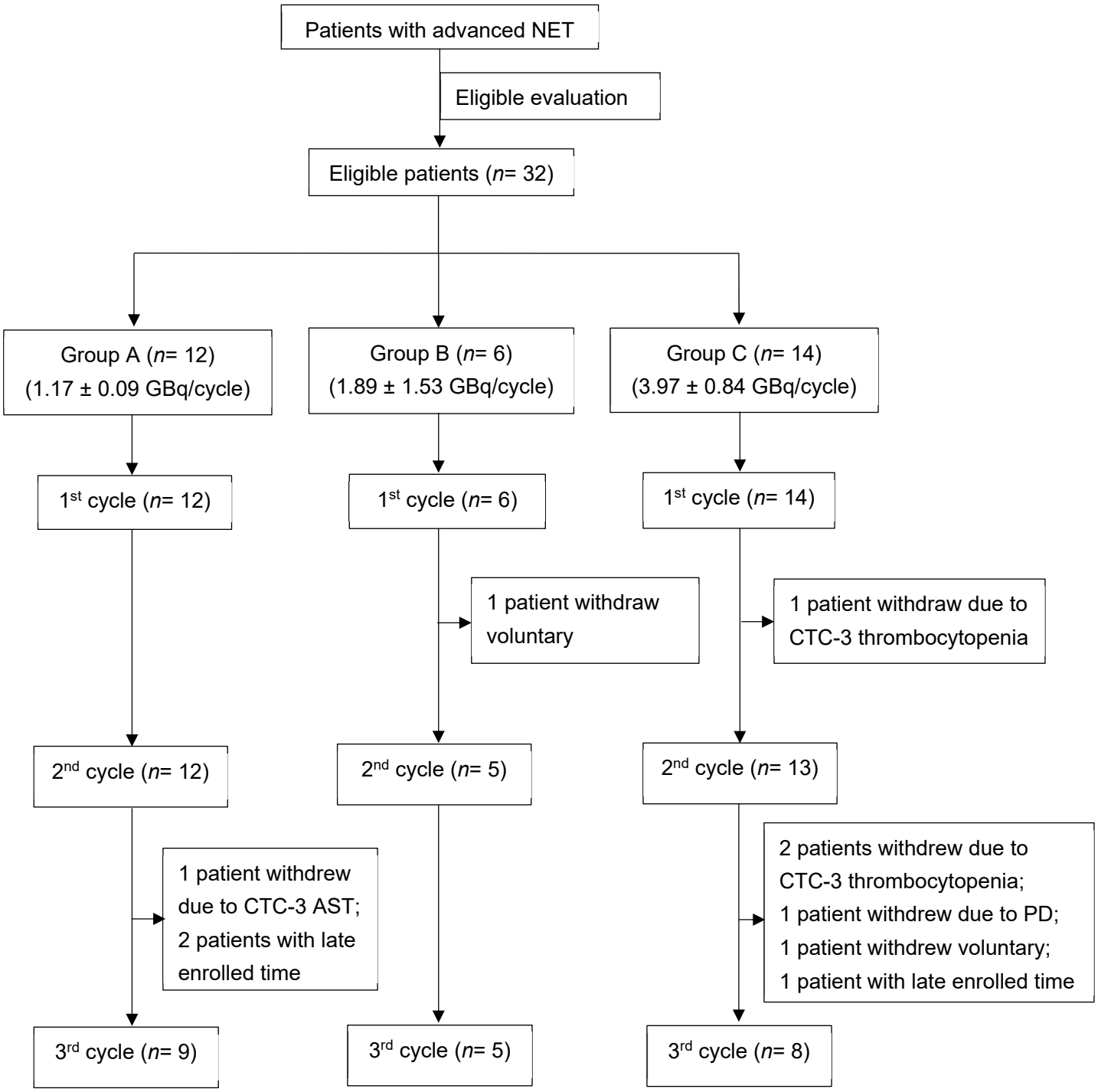

Fig 1. Participants flow chart of groups A-C.

PD: progressive disease

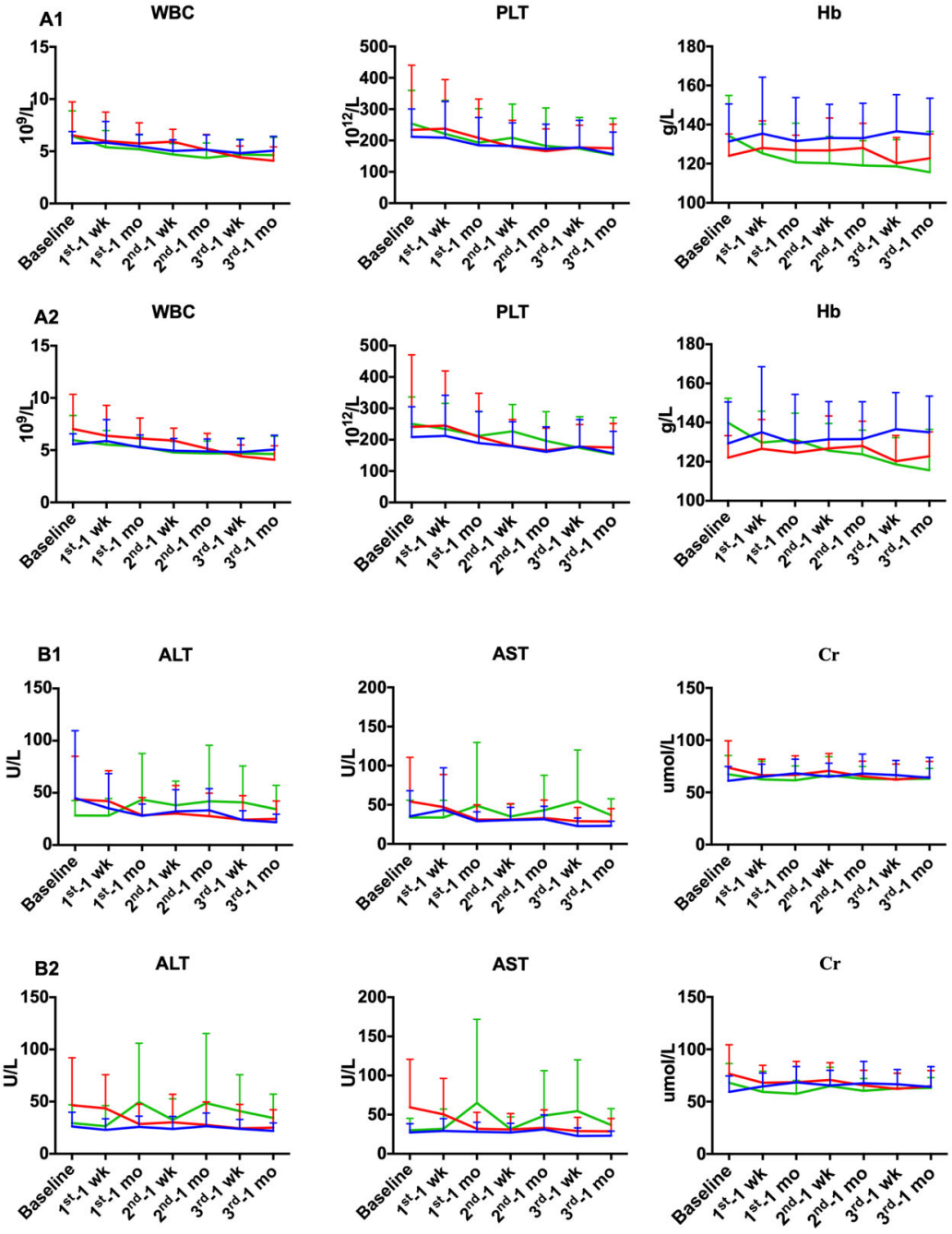

Fig 2. The changes of WBC, Hb, PLT, ALT, AST and Cr at baseline, 1 week and 4 weeks after each cycle of PRRT. **(A1, B1):** all the patients; **(A2, B2):** patients who completed 3 cycles of PRRT. Blue line = group A; red line = group B; green line = group C.

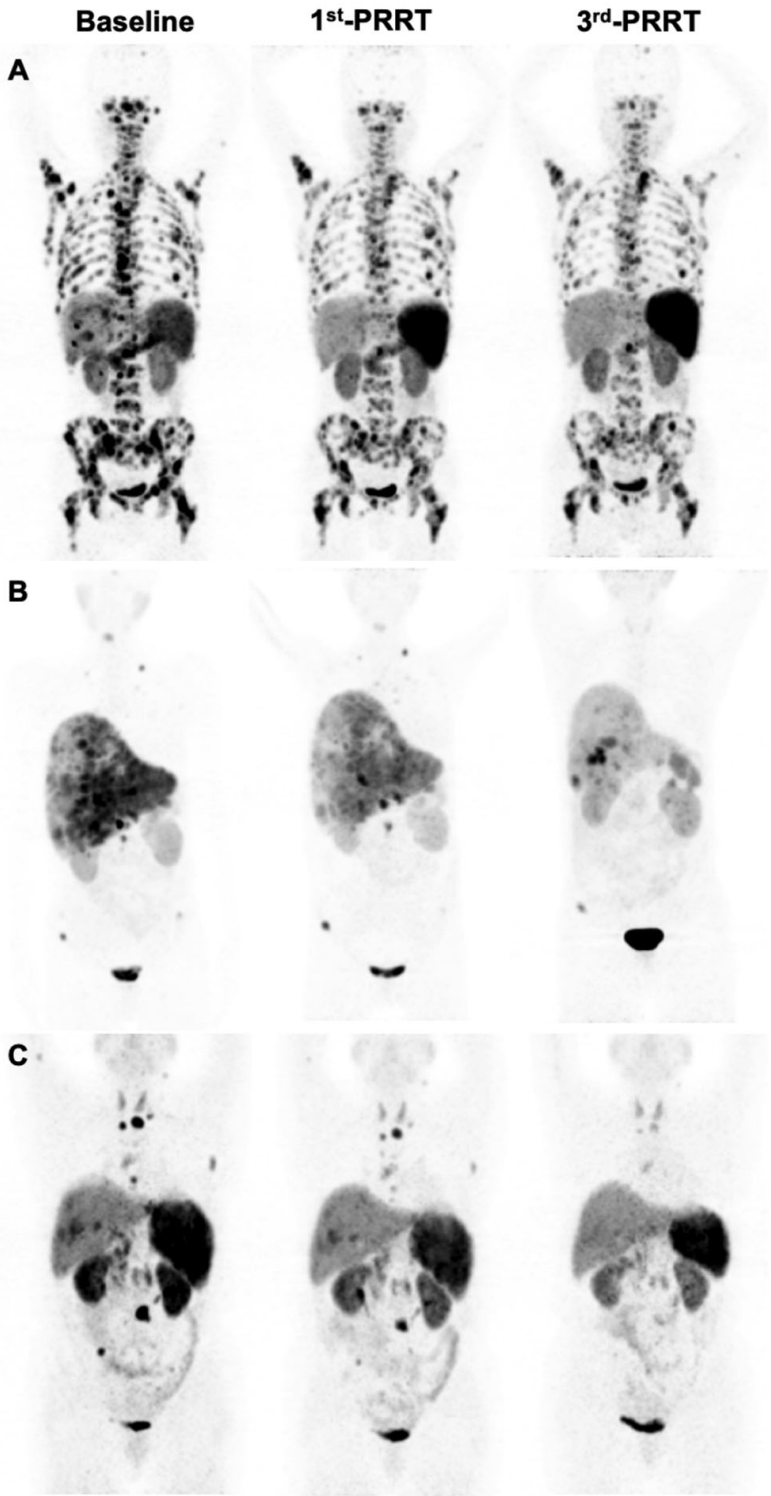

Fig 3. Representative images of partial remission. (A) group A; (B) group B; (C) group C.

Table 1. Baseline demographic and clinical characteristics of patients

Characteristic	Group A (n= 12)	Group B (n= 6)	Group C (n= 14)
Male/Female	7/5	4/2	7/7
Age-y	53±13	55±10	50±10
Primary tumor site			
Pancreas	3	3	7
Stomach	1	0	0
Duodenum	1	1	3
Rectum	2	0	2
Lung	1	1	0
Ovary	0	0	0
CUP	0	0	1
MEN1	0	1	0
Paraganglioma	2	0	1
Pheochromocytoma	2	0	0
Tumor grade			
Grade 1	3	1	3
Grade 2	9	4	10
Grade 3	0	1	1
Number of lesions			
1-10	4	2	6
11-20	2	2	1
>20	6	2	7
Metastases			
Liver	9	5	14
Bone	8	2	6
Lymph nodes	7	2	5
Lung	2	1	3
Prior treatment			
Surgery	9	2	7
Somatostatin analog	8	5	5
Everolimus	2	3	1
Tyrosine kinase inhibitor	1	5	9
Chemotherapy	2	3	6
Radiotherapy	1	1	1
TACE	1	1	3
Disease course(mo)	58±64	58±26	55±25

CUP: carcinoma of unknown primary; MEN 1: multiple endocrine neoplasia; TACE: transarterial chemoembolization

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