The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors: A meta-analysis

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Abstract
Background: Somatostatin analog therapies showed great potential for patients suffering advanced neuroendocrine tumors (NETs). This study was aimed to evaluate the therapeutic efficacy of 177Lu-DOTATATE/DOTATOC (177Lu-octreotate/octreotide) peptide receptor radionuclide therapy (PRRT) in advanced or inoperable NETs patients.

Methods: PubMed, Web of Science, Embase and Cochrane Library were searched from 1950 to April 2019. Eligible studies should include randomized or nonrandomized controlled trials (RCTs)-based investigations of 177Lu-octreotate/octreotide PRRT for NETs. All these studies were assessed with Response Evaluation Criteria in Solid Tumors (RECIST), RECIST 1.1, Southwest Oncology Group (SWOG) criteria or World Health Organization (WHO) criteria. Disease response rates (DRRs) and disease control rates (DCRs) were calculated according to each response criteria group. DRRs were defined as the percentages of patients with complete response (CR) + partial response (PR), while DCRs represented the percentages of patients with CR+ PR+ stable disease (SD). The pooled proportions were calculated with either a fixed-effects model or a random-effects model depending on the test for heterogeneity.

Results: A total of 22 studies (1758 patients) were included in this meta-analysis: 8 studies with 478 patients met RECIST criteria, 10 studies with 1127 patients met RECIST 1.1 criteria, 5 studies with 459 patients met SWOG criteria, and 1 study with 40 patients met WHO criteria, and among these articles 1 study met both RECIST and RECIST 1.1 criteria and 1 met both RECIST 1.1 and SWOG criteria. The pooled DRRs were 33.0% (95% CI: 25.0%-42.0%, I² = 65%), 35.0% (95% CI: 26.0%-45.0%, I² = 91%) and 25.0% (95% CI: 14.0%-36.0%, I² = 84%) according to RECIST, RECIST 1.1 and SWOG criteria, respectively. The pooled DCRs were 79.0% (95% CI: 75.0%-83.0%, I² = 97%), 83.0% (95% CI: 78.0%-88.0%, I² = 0) and 82.0% (95% CI: 75.0%-89.0%, I² = 91%), respectively.

Conclusion: In advanced NETs patients, DRRs and DCRs were significantly elevated after initial treatment with 177Lu-DOTATATE PRRT, which shows that this treatment would be beneficial and promising for advanced or inoperable NETs patients.

Abbreviations: 177Lu-DOTATATE/DOTATOC = 177Lu-octreotate/octreotide, DCRs = disease control rates, DRRs = disease response rates, NETs = neuroendocrine tumors, PFS = progression free survival, PRISMA = preferred reporting items for systematic reviews and meta-analysis, PRRT = peptide receptor radionuclide therapy, RECIST = response evaluation criteria in solid tumors, SWOG = Southwest Oncology Group, WHO = World Health Organization.

Keywords: 177Lu-DOTATATE/DOTATOC, advanced neuroendocrine tumors, meta-analysis, neuroimaging, positron emission tomography

1. Introduction

Heterogeneity and slow-growth are the main characteristics of neuroendocrine tumors (NETs).[1,2] They used to be defined as rare malignancies, but in the past 3 decades, the prevalence of NETs raised approximately 5 folds in the United States.[3] A study in 2008 based on the data of Surveillance, Epidemiology, and End Results (SEER) program registries showed that the incidence of NETs elevated from 1.09/100000 to 5.25/100000 from 1973 to 2003.[4] As a result, the perception and treatment of NETs drew oncologists and researchers’ great attention in the past 15 years.[5] As for NETs patients with operable and localized focus, the first choice is surgical resection. However, tumors of this type are usually diagnosed in the late-phase due to the slow-growing nature and the nonspecific signs which make surgical resection impossible.[6]

Most NETs cell membrane overexpressed somatostatin receptor which was emphasized as the target for peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin.[7] In 1990s, radiolabeled somatostatin analogues 111In-octreotide, was first applied in NETs therapy.[8] Since then, more radionuclide tracers have been used for NETs treatment such as 90Y and...
177Lu-octreotate/octreotide (DOTATATE/DOTATOC) PRRT, generated from ytterbium (Yb), is capable of delivering precise low dosages of β energies between 0.149 and 0.479 MeV with ranges of tissue penetration between 0.5 to 2.0 mm, and this property endows 177Lu-octreotate/octreotide with limited collateral damage to the normal tissues compared with 90Y. In addition, 177Lu has 2 main γ-emission energies, 0.113 MeV (relative abundance 6%) and 0.208 MeV (11%), thereby being provided as the adequate radiotracer for scintigraphic imaging during and after therapy, biodistribution, and dosimetry studies. In 2015, Kim et al reviewed the efficacy of 177Lu-octreotate/octreotide PRRT and found that this treatment was very effective in inoperable or metastatic NETs patients. Nevertheless, only single center trials were enrolled in the review. By far, there have been more single center trials and several multicentre randomized trials such as NETTER-1 about 177Lu-octreotate/octreotide PRRT in NETs. In this article we addressed and analyzed the efficacy and benefit of 177Lu-labeled PRRT for advanced NETs in recent years.

2. Materials and methods

2.1. Statement

This meta-analysis was based entirely on previous published studies which had declared ethical approvals and no original clinical raw data was collected or utilized, thereby ethical approval was not conducted for this study. This review was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), and the PRISMA checklist is shown in Table 1.

2.2. Search and selection strategy

An independent review of the PubMed, Cochrane Library, Web of Science, and Embase data bases was performed from Jan 1, 1950, to Apr 30, 2019. The search was implemented by using the following keywords “Neuroendocrine Tumors” and “177Lu-DOTATATE/DOTATOC”. The complete search phrases used for PubMed were: (“DOTA” AND (“177Lu” OR “Lu177” OR “Lu-177” OR “177-Lu”) AND (“neuroendocrine tumors” [MeSH Terms] OR “Neuroendocrine neoplasm”[Text Word] OR “Neuroendocrine Tumor”[Text Word] OR “Neuroendocrine carcinoma”[Text Word]). The searched articles were screened by Lin Lin and Meng-jiao Wang independently. Full texts were retrieved if they were confirmed to the eligibility criteria. If there were duplicates (patients’ data from the same trial or institution), only the most complete, recent and relevant study was selected.

2.3. Inclusion and exclusion criteria

Inclusion criteria were as follows: randomised clinical trials (patients >10) with the utility of 177Lu-DOTATATE/DOTATOC product...
(177)Lu-octreotate/octreotide) PRRT in adults with NETs. Exclusion criteria: randomised clinical trials (patients < 10), case reports, review articles, meetings, news, conferences, abstracts and editorials.

### 2.4. Data extraction and primary outcomes

The data were extracted by 2 reviewers (Lin Lin and Meng-jiao Wang), independently. The following information was collected from each trial: first author, number of patients, treatment compound, dosages of radiopharmaceuticals, treatment cycles, radiopharmaceuticals’ cumulative activities and response criteria. The primary outcomes were disease response rates (DRRs) and disease control rates (DCRs). The definitions of DRRs and DCRs were described previously (DRRs = proportions of patients with complete response (CR) + partial response (PR), DCRs = proportions of patients with CR+ PR+ stable disease (SD).[12] Overall survival (OS) and progression free survival (PFS) were not assessed because most of the trials were single-arm trials.

### 2.5. Statistical analysis

We used the Review Manager (version 5.3) for statistical analyses. The efficacy of 177Lu-octreotate/octreotide treatment was assessed depending on 2 indicators: DRRs and DCRs. A Cochran Q test was used to assess heterogeneity between studies and I² statistic was used to show the magnitude of the heterogeneity. For categorical variables, the pooled estimation of effects was calculated with a random-effects model or a fixed-effects model. If I² value >50%, a random-effects model was used, otherwise we use a fixed-effects model. Funnel plots were performed to assess the potential publication bias. A 2-tailed P value of less than .05 was considered statistically significant.

### 3. Results

#### 3.1. Study characteristics

We identified a total of 716 articles, and thereof 148 conference reports/editorials/meetings/news and 445 reviews/case reports (patients < 10)/comments/abstracts were excluded. The remaining 123 potentially relevant publications were retrieved for detailed assessment, and 64 studies were excluded because the research subjects were irrelevant. After a further detailed review of the remained 59 articles, 37 articles were excluded for inadequate data or duplicated data, and 22 studies including 1758 patients were eligible for inclusion criteria. The flow chart is shown in Figure 1. For each selected study, data quantification was completely assessed.
In this meta-analysis, tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), RECIST 1.1, Southwest Oncology Group (SWOG) criteria, World Health Organization (WHO) criteria, or more than one criterion. 8 studies were evaluated by RECIST. 10 trials were evaluated by RECIST 1.1. Five trials were based on SWOG criteria. One trial was assessed by WHO criteria. There were 2 articles evaluated by 2 criteria, of them 1 by RECIST and RECIST 1.1, the other by RECIST 1.1 and SWOG. The characteristics of these trials are shown in Table 2.

### 3.2. DRRs and DCRs

Detailed data of these selected studies data, DRRs and DCRs are demonstrated in Table 3. The pooled rates were presented with a random-effects model or a fixed-effects model on the basis of magnitude of the heterogeneity. There was only 1 article evaluated by WHO criteria, so it was not included in the following assessment.

#### 3.2.1. RECIST criteria group

For RECIST criteria, 8 studies with 478 patients were analyzed. As shown in Figure 2, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 65\%, P = 0.006$). DRRs ranged between 16.7% and 53.0%. The random-effects model showed a pooled effect of 33.0% (95% CI: 25.0%-42.0%) for DRRs. As for DCRs, the test for heterogeneity performed no statistical significance ($I^2 = 0\%, P = 0.62$). DCRs ranged from 72.0% to 100%. The pooled effect was 79.0% (95% CI: 75.0%-83.0%) for DCRs according to the fixed-effects model.

#### 3.2.2. RECIST 1.1 criteria group

For RECIST1.1 criteria, 10 studies with 1127 patients were analyzed. As shown in Figure 3, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 91\%, P < 0.001$). DRRs ranged between 10.0% and 65.0%.

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### Table 2

**List of study characteristics.**

| First author       | No. of total patients | Treatment compound | Dose (GBq) | 177 Lu cycles | Cumulative activity (GBq) | Median follow-up, mo | Response criteria |
|--------------------|-----------------------|--------------------|------------|--------------|--------------------------|----------------------|------------------|
| Garkavij 2010 (17) | 12                    | DOTATATE           | 7.4        | 3–4          | 26 (17–45)               | 4–24                 | RECIST           |
| Swärd 2010 (21)   | 16                    | DOTATATE           | 8          | 3 (1–5)      | –                        | 5                    | RECIST           |
| Romero 2014 (20)  | 16                    | DOTATOC            | 7.4        | 1–5          | 13.5±6.5                 | 9 (1.0–80.1)         | RECIST           |
| Hamidittabor 2017 (18) | 28            | DOTATATE           | 7.4        | 4            | 29.6                     | 12.3 (2.5–49)        | RECIST           |
| Delpassand 2014 (16) | 32               | DOTATATE           | 7.4        | 2–4          | 29.6                     | 16.11 (3–26.8)       | RECIST           |
| Bodei 2011 (15)   | 51                    | DOTATATE           | 3.7–7.4    | 4–6          | 25.2–29.2                | 60                   | RECIST           |
| Latteigård 2019 (19) | 79           | DOTATATE           | –          | 4 (1–10)     | –                        | 45 (6–99)            | RECIST/RECIST 1.1 |
| van Wiet 2013 (22) | 257               | DOTATATE           | 3.77±4.4   | 4            | 22.2–29.6                | –                    | RECIST/SWOG       |
| Limouris 2016 (28) | 13                   | DOTATATE           | 6.8        | 3–6          | 58 (13–77)               | 4.24                 | RECIST 1.1       |
| Paghane 2017 (29) | 19                    | DOTATATE           | 5.55       | 1–5          | –                        | –                    | RECIST 1.1       |
| Zandee WT 2019 (31) | 34               | DOTATATE           | 7.4        | 4            | 7.4–29.6                 | 18.1 (3·35–37)       | RECIST 1.1       |
| Kalshetty 2018 (27) | 46             | DOTATATE           | 5.55       | 4–5          | –                        | 1·5–4                | RECIST 1.1       |
| Demirci 2018 (25) | 160                  | DOTATATE           | 3.7–8.1    | 3–12         | –                        | 30.6                 | RECIST 1.1       |
| Baum 2016 (23)    | 32                   | DOTATOC            | 3.5–10.0   | 2–4          | 3.5–29.2                 | 16·1±12.4            | RECIST 1.1       |
| Stroebger 2017 (30) | 101            | DOTATOC            | 7.4        | 4            | 29.6                     | 14                   | RECIST 1.1       |
| Garske-Román 2018 (26) | 200          | DOTATATE           | 7.4        | 1–10         | 29.6 (5–74)              | 31 (1–68)            | RECIST 1.1       |
| Brander 2017 (24) | 443                  | DOTATATE           | 7.4        | 4            | 27.8–29.6                | 63 (55–72)           | RECIST 1.1       |
| Ianniello 2015 (33) | 15               | DOTATATE           | 3.7        | 4–5          | 21.5 (12.9–27.8)         | 29 (7–69)            | SWOG             |
| Paganelli 2014 (34) | 43             | DOTATATE           | 3.7/5.5    | 5            | 18.45/27.8               | 25 (7–50)            | SWOG             |
| Sansovini 2017 (35) | 60              | DOTATATE           | 3.7/5.5    | 5            | 18.5/27.8               | 59 (6.5–97)          | SWOG             |
| Ezziddin 2014 (32) | 74                   | DOTATATE           | 7.9        | 4            | –                        | 47 (44.5–49.5)       | SWOG             |
| Danthala 2014 (14) | 40                  | DOTATATE           | 7.4        | 1–6          | 7.4–44.4                 | 6·2–50.2             | WHO              |

RECIST = response evaluation criteria in solid tumors, SWOG = southwest oncology group, WHO = World Health Organization.
69.0%. The random-effects model showed a pooled effect of 35.0% (95% CI: 26.0%-45.0%) for DRRs. As for DCRs, the test for heterogeneity presented statistical significance ($I^2 = 77\%$, $P < .001$) among these articles. DCRs ranged from 68.0% to 93.8%. The pooled effect was 83.0% (95% CI: 78.0%-88.0%) for DCRs according to the random-effects model.

### 3.2.3. SWOG criteria group.

For SWOG criteria, 5 studies with 459 patients were analyzed. [22,32–35] As shown in Figure 4, the test for heterogeneity showed heterogeneity for DRRs ($I^2 = 84\%$, $P < .001$). DRRs ranged between 7% and 36.5%. The random-effects model showed a pooled effect of 25.0% (95% CI: 14.0%-36.0%) for DRRs. For DCRs, the test for heterogeneity showed some significance ($I^2 = 66\%$, $P = .02$) among these articles. DCRs ranged from 74.0% to 89.2%. The pooled effect was 82.0% (95% CI: 75.0%-89.0%) for DCRs according to the random-effects model.

### 4. Discussion

In this meta-analysis, 22 high-quality published articles containing 1758 inoperable or metastatic NETs patients who adopted $^{177}$Lu-labelled PRRT were included. The evaluation of treatment efficacy was performed by RECIST or RECIST 1.1 or SWOG. The results showed that the pooled effects of DRRs were 33.0% (95% CI: 25.0%-42.0%) by RECIST, 35.0% (95% CI: 26.0%-45.0%) by RECIST 1.1 and 25.0% (95% CI: 14.0%-36.0%) by SWOG, while the DCRs were 79.0% (95% CI: 75.0%-83.0%) by RECIST, 83.0% (95% CI: 78.0%-88.0%) by RECIST 1.1 and 82.0% (95% CI: 75.0%-89.0%) by SWOG. Based on these
Figure 3. Forest plots of proportions of disease response rates (A) and disease control rates (B) in RECIST 1.1 criteria group. RECIST = response evaluation criteria in solid tumors.

Figure 4. Forest plots of proportions of disease response rates (A) and disease control rates (B) in SWOG criteria group. SWOG = southwest oncology group.
results, we concluded that \(^{177}\)Lu-labelled PRRT displayed encouraging treatment efficiency for advanced NETs.

Meanwhile, \(I^2\) statistical test demonstrated significant heterogeneity among the studies in different criteria groups with an exception of the analysis of DCRs in RECIST criteria group. The heterogeneity may be attributed to differences in basic characteristics of the study populations, locations of the study, drug compliance in each study, batch of drug and correction of relevant factors. Due to the limited information in individual studies, subgroup analysis or meta-regression were not applicable to assay the sources of heterogeneity in this meta-analysis. In consequence, the results of this analysis should be interpreted with caution especially when extrapolation was considered.

Recently, a phase III clinical trial (NETTER-1) designed for evaluating the efficacy and safety of \(^{177}\)Lu-DOTATATE PRRT in patients with advanced, SSTR positive and G1/G2 midgut NET has published their stage results.\(^{100}\) At the data cutoff date for the cohort, compared to the control group (high-dose octreotide long-acting repeatable group), \(^{177}\)Lu-DOTATATE group had more patients survived more than 20 months (65.2% vs 10.8%). The DRR, evaluated by RECIST 1.1, was 18% in the \(^{177}\)Lu-DOTATATE group while in the control group it was 3% (\(P<.001\)). Another large clinical trial with over 200 patients treated with \(^{177}\)Lu-DOTATATEPRRT showed that the quality of life and symptoms were improved in 40% to 70% of cases depending on the preexistence of a certain condition.\(^{116}\) Strosberg et al found that compared with the control group (high-dose octreotide long-acting repeatable group), \(^{177}\) Lu-DOTATATE PRRT group demonstrated a longer PFS (28.4 months vs 8.5 months).\(^{117}\) Altogether, repeated cycles of \(^{177}\)Lu-DOTATATE PRRT provided an obvious improvement of the quality of life and prolonged the patients’ survival time.

There was no obvious acute toxicity during or immediately after the \(^{177}\)Lu-DOTATATE treatment. The maximum toleration of this treatment was up to 29 GBq cumulative activity (up to 7.4 GBq/cycle) with minimal hematological or renal damage.\(^{115,115}\) In a study by Danthala et al, there was no significant impact on white blood cells or platelets and no renal toxicity was observed during PRRT with \(^{177}\)Lu-DOTATOC and 24 months after treatment.\(^{114}\) Nausea and vomiting were the most common side effects, followed by transient skin redness.\(^{116}\) Delpassand et al. found that hematological toxicity and bone metastasis may occur after the repeated cycles of \(^{177}\)Lu-DOTATATE PRRT, and these side effects were associated with the prior history of chemotherapy treatment.\(^{116}\)

5. Conclusion

This meta-analysis demonstrated that the curative effect of repeated treatment with \(^{177}\)Lu-octreotate/octreotide PRRT was promising in advanced NETs patients. Up to date, there are still several clinical studies in progression, so we will get more information to validate this therapeutic modality.

Author contributions

Data curation: Lin Lin, Meng-jiao Wang.

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