

Treatment of Neuroendocrine Tumors (NETs) Using Somatostatin Analogs: Current View, Clinical Achievements and Future Perspectives

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Abstract

Neuroendocrine tumors (NETs), previously known as carcinoid tumors, are a heterogeneous group of neoplasms which originate from cells of the endocrine or nervous system with an overall incidence of 1-5 cases per 100,000 individuals per year. Recent studies showed that their incidence has dramatically increased worldwide over the last few years. The majority of NETs overexpress the somatostatin receptors (SSTRs) in tumor cells which are further being used as the important targets for therapy purposes using somatostatin analogs (SSAs) such as octreotide and lanreotide. Like native somatostatin, SSAs bind to SSTRs and induce a range of cellular effects, including antitumor activity. Antitumor activity of SSAs and their high binding properties for the SSTRs have become valuable tools for developing advanced treatment of NETs. Consequently, SSAs have been used widely in routine clinical practice, especially for treatment of various types of NETs. Despite treatment using SSAs have made a positive contribution, recent development suggests that the used of SSAs in combination with chemotherapy or peptide receptor radionuclide therapy (PRRT) can improve clinical outcome in patients with NETs. This review provides an overview of the recent trend in the treatment of NETs using SSAs, their clinical achievements in the last few years and their potential applications in the future.

Keywords: *neuroendocrine tumors, treatment, somatostatin analogs, chemotherapy, PRRT*

INTRODUCTION

Neuroendocrine tumors (NETs), previously known as carcinoid tumors are a heterogeneous group of neoplasms which originate from cells of the endocrine or nervous system and may derive from the embryonic neural crest cells of several organs (Kaltsas, *et al.*, 2004; Gould, *et al.*, 2013; Al-Chalabi, *et al.*, 2018). Most NETs are located in the gastrointestinal tract and the lung and occasion-

ally occur in the pancreas, head and neck region, prostate, ovary, testis and liver (Gabriel, *et al.*, 2007; Modlin, *et al.*, 2003). Interestingly, NETs can also be found in the breast tissue, although the incidence

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is rare, around 0.27–0.50% (Adams, *et al.*, 2014). Despite pathophysiological mechanism underlying NETs is still largely unknown, study at the genomic level has suggested the important role of transcriptome, micro-RNome and exome in the regulation of secretory and proliferative mechanism of NETs (Kidd, *et al.*, 2015). In addition, several hypotheses including dysregulation of the phosphatidylinositol-3-kinase (PI3K)/AKT and the mammalian target of rapamycin (mTOR) signaling have been linked with the pathogenesis of these tumors (Boora, *et al.*, 2015).

NETs are characterized by their ability to overexpress the neurosecretory granules that contain numerous bioactive compounds such as peptides, hormones, kinins, vasoactive amines, and endorphins which cause characteristic hormonal syndromes leading to several clinical signs and symptoms (Gould, *et al.*, 2013; Yao, *et al.*, 2008). A variety of clinical symptoms in NETs patients may include flushing, diarrhea, bronchospasm, hepatomegaly, sweating, hemoptysis, wheeze, hypotension and anxiety (Bodei, *et al.*, 2014; Jayasena, *et al.*, 2013). Additionally, local symptoms induced by tumor aggregates (*e.g.*, pain, bleeding, obstruction, and perforation) are frequently observed in patients with advanced NETs (Frilling, *et al.*, 2014). Importantly, the majority of NETs overexpress somatostatin receptors (SSTRs), mainly types 2 and 5 on their cell surfaces which are further being used as the important targets for therapy of patients with NETs and neuroendocrine neoplasias (NENs) (Kayani, *et al.*, 2008; García-Talavera, *et al.*, 2014; Fani, *et al.*, 2017).

It was previously believed that NETs are relatively slow growing and uncommon in humans with an overall incidence of 1–5 cases per 100,000 per year (Amr, *et al.*, 2015; van der Zwan, *et al.*, 2013). However, a large number of reports showed that their incidence has dramatically increased worldwide over the last few years. According to Surveillance Epidemiology and End Results (SEER) database, in 1973 the incidence of NETs was 1.09 per 100,000. This incidence increased 5–

fold in 2004 to 5.25 per 100,000 (Yao, *et al.*, 2008). Furthermore, the project of surveillance of rare cancer (RARECARE) also found that the overall incidence rate of NETs in Europe was 25 per 1,000,000 during 1978–2002 (van der Zwan, *et al.*, 2013).

In the United Kingdom during 1971–2006, the incidence of NETs rose approximately 2.9– to 3.8-fold (Frilling, *et al.*, 2014). In particular, since the 1970s, the incidence of pancreatic endocrine tumor (pNET) also increased annually from 0.32 to 0.43 per 100,000 (Dilz, *et al.*, 2015). Korse *et al.* reported that the incidence of grade 1 NET (G1NET) in the Netherlands has progressively increased from 2 per 100,000 in 1990 to 3 per 100,000 in 2010 and the large increase experienced by grade 2 NET (G2NET) from 0.01 per 100,000 in 1990 to 0.2 per 100,000 in 2010 (Korse, *et al.*, 2013). Another report showed that in Denmark, the incidence of NETs increased by 2-fold in men from 0.24 to 0.53 per 100,000 per year (Skuladottir, *et al.*, 2002). In Australia, the annual incidence of NETs increased approximately 2-fold from 1.7 (1980–1989) to 3.3 (2000–2006) (Luke, *et al.*, 2010).

An important progress in the field of NETs management was the recent development of several therapeutic strategies that exploit the role of somatostatin and its analogs, which seemed to become an attractive option in routine clinical practice (Rai, *et al.*, 2015). Although the application of somatostatin analogs (SSAs) is a well established treatment for various types of NETs, the combination of SSAs with other therapies has not been extensively studied. Thus, current development in preclinical and clinical studies of SSAs for treatment of NETs and their combination with chemotherapy and peptide receptor radionuclide therapy (PRRT) as well as the potential future of therapeutic applications are discussed here.

Somatostatin and Somatostatin Receptors (SSTRs)

Somatostatin, also known as somatotropin release-inhibiting factor is a naturally occurring peptide hormone that controls the endocrine and

NETs Treatment using Somatostatin Analogs (SSAs)

Initially, surgery is the established treatment and has been used for a long time to remove NETs and prolong survival rate in patients (Kaltsas, *et al.*, 2004; Ha, *et al.*, 2012; Walter, *et al.*, 2012). This treatment has also been used in patients with liver metastasis which arises from carcinoid tumors (Pathak, *et al.*, 2013; Nave, *et al.*, 2001). A study showed that surgery for cytorreduction of NET metastasis has been associated with the duration of survival, for instance Mayo and colleagues reported that a 5-year survival and 10-year survival of 74% and 51% respectively, were achieved by the patients after liver-directed surgery for metastatic NETs (Mayo, *et al.*, 2010). However, the surgery outcome is directly depending on the stage of tumors (tumor size) (Ha, *et al.*, 2012), tumor location, and involvement of surrounding tissues (Ober, 2012).

Another treatment to destroy the tumor aggregates of NETs is chemotherapy. This approach has traditionally been used in a variety of NETs. The use of combination chemotherapeutic agents, such as 5-fluorouracil and streptozotocin generated an overall disease control (ODC) rate of 83.3% in 96 patients with pNET (Dilz, *et al.*, 2015). Moreover, single agent for NETs therapy such as adriamycin, 5-fluorouracil, actinomycin-D and dacarbazine demonstrated an objective response (OR) of 21, 26, 6, and 13%, respectively (Moertel, 1983). In NETs, the efficacy of chemotherapy is always associated with the types of NETs, for example, pNETs have a high sensitivity to chemotherapy, whereas gastrointestinal NETs (GINETs) are often resistant to chemotherapy treatment (Walter, *et al.*, 2012). Moreover, due to the toxicity, some chemotherapy agents may be not suitable for some patients and therefore limit their use in clinical setting (Peixoto, *et al.*, 2014).

NETs management has evolved over the last few decades due to the increasing understanding of their tumor biology and molecular regulation.

Some studies have been showed that somatostatin has a broad range of biological functions such as antiproliferative regulation (Owonikoko, *et al.*, 2019), induction of apoptosis to inhibit tumor cell proliferation and angiogenesis (Rai, *et al.*, 2015), regulation of endocrine and exocrine secretions including growth hormone in acromegaly, inhibition the secretion of insulin and glucagon (Murray, *et al.*, 2015) and inhibition of the release of gastrointestinal hormones and thyroid-stimulating hormone (Theodoropoulou, *et al.*, 2013).

The inhibitory effects of several hormones and growth factors as well as tumors growth factor are making somatostatin as a crucial tool for developing advanced treatments of patients with NETs. Commonly, the effect of somatostatin as an antitumor in NETs is based on their capability to exert antitumor activity through direct and indirect mechanisms (He, *et al.*, 2019). The direct mechanisms include some biological processes in the cell such as induction pertussis toxin-sensitive, G-protein-coupled receptor (GPCR) intracellular signals, proapoptotic effect, and inhibition cell cycle (Chalabi, *et al.*, 2014). One of the main processes in the indirect mechanisms of somatostatin is the inhibition of growth factor receptor signaling. In this process, protein tyrosine phosphatases (PTPs) has played an important role by dephosphorylating the growth factor in tyrosine kinase receptors (Theodoropoulou, *et al.*, 2013).

On the other hand, somatostatin also exerts a number of indirect antitumor mechanisms such as inhibition of the secretion of hormones and growth factors, inhibition of the cell proliferation and angiogenesis by eliminating somatostatin receptor function, and modulation of the immune system to stimulate natural antitumor mechanism (Susini, *et al.*, 2006; Chalabi, *et al.*, 2014). However, somatostatin has a short half-life ($t_{1/2}$) *in vivo* (1–3 minutes), making it unsuitable for the treatment of NETs, hence some synthetic SSAs were developed including octreotide, lanreotide, vapreotide (Figure 2) (Marciniak, *et al.*, 2017). To date, SSAs have

been used to treat most NETs either for inhibiting the tumor growth or symptom relief (Cwikla, *et al.*, 2015; Maqsood, *et al.*, 2019).

Similar to native somatostatin, SSAs bind to SSTRs and induced a range of cellular effect, including antitumor activity (Sideris, *et al.*, 2012). Octreotide was the first SSA approved and widely used for management of hormonal syndromes resulting from NETs. This analog has a strong affinity to SSTR-2 and SSTR-5 and showed antitumor properties in patients with NETs. Accumulating evidence showed octreotide long-acting repeatable (LAR) as well as lanreotide autogel (lanreotide ATG) have strong efficacy and well tolerated in NET patients (Godara, *et al.*, 2019). In a clinical

study by Rinke, *et al.*, it was clearly demonstrated that treatment of NETs patients using octreotide LAR resulted in a median time to tumor progression of 14.3 months, higher than placebo groups (6 months). Additionally, stable disease was achieved in 66.7% of patients in the octreotide LAR group after 6 months of treatment. This number was higher than patients in placebo group (37.2%) (Rinke, *et al.*, 2009). Antiproliferative effects of lanreotide ATG has also been demonstrated in the efficacy and safety study in 30 patients with well-differentiated NETs. In this study, lanreotide ATG provided effective tumor stabilization in 24 patients (89%) and median progression-free survival (PFS) of 12.9 months (Richard, 2013).

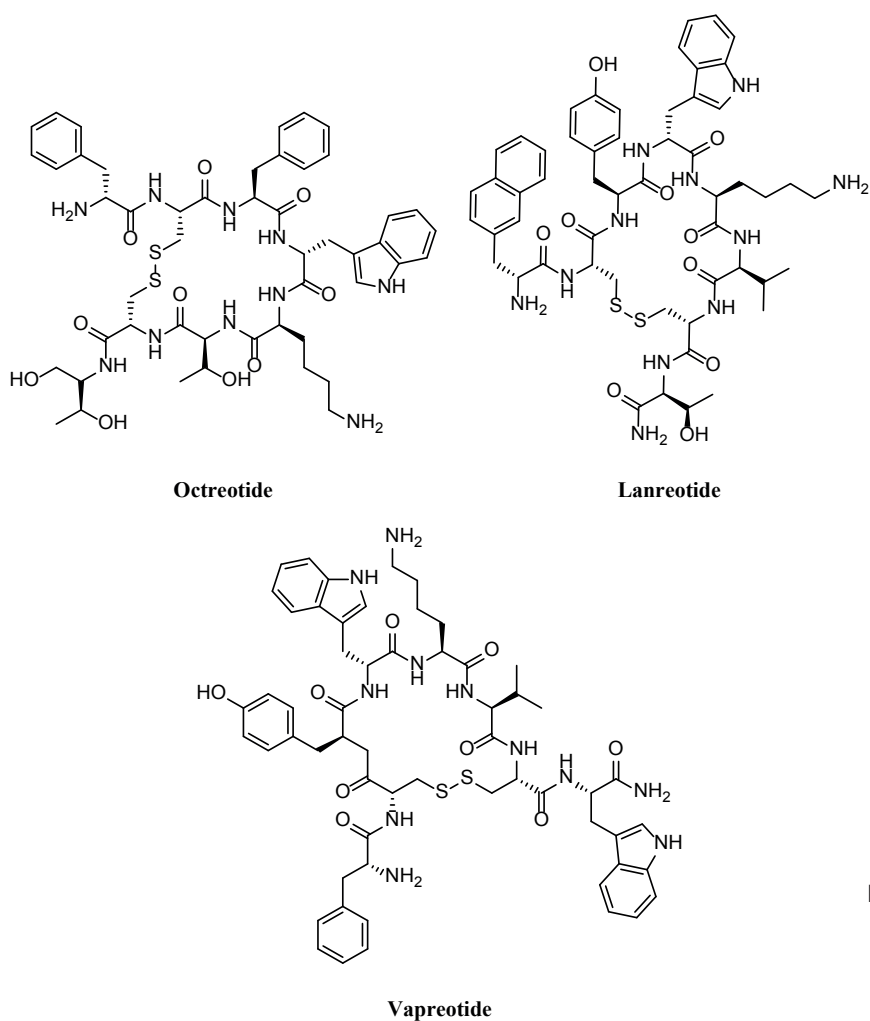


Figure 2. Chemical structure of several somatostatin SSAs (Gunther, *et al.*, 2018).

Peptide Receptor Radionuclide Therapy (PRRT)

To date, some SSAs have also been exploited as PRRT for eradicating malignant cells in NETs. PRRT is a treatment that uses radioisotope attached to the SSA to deliver therapeutic dose of ionizing radiation to tumor cells (Dash, *et al.*, 2015). The illustration of the PRRT mechanism to eradicate tumor cells is shown in Figure 3.

In the past ten years, some PRRT SSTR-targeting radionuclide therapies for clinical management of NETs were developed, including ^{90}Y -[DOTA⁰, Tyr³]-octreotide (^{90}Y -DOTA-TOC), ^{90}Y -[DOTA⁰, Tyr³]-octreotate (^{90}Y -DOTA-TATE), ^{177}Lu -[DOTA⁰, Tyr³]-octreotide (^{177}Lu -DOTA-TOC), ^{177}Lu -[DOTA⁰, Tyr³]-octreotate (^{177}Lu -DOTA-TATE) (Gabriel, *et al.*, 2007; Baum, *et al.*, 2015). The idea of using ^{90}Y ($t_{1/2} = 64.6$ hours) and ^{177}Lu ($t_{1/2} = 160.8$ hours) as radionuclide therapy is based on their energy characteristics. ^{177}Lu emits β^- -energy of 149 keV and maximum particle range of 1.5 mm, and therefore suitable for destroying small lesions of NETs. In contrast, ^{90}Y emits higher β^- energy of 2.28 MeV and maximum particle range of 12 mm which more suitable for the eradication of bulky NETs. These characteristics make them well suited for PRRT of NETs (Perk, *et al.*, 2005; Garkavij, *et al.*, 2010; Fenwick, *et*

al., 2014). However, the combination of ^{90}Y and ^{177}Lu may be the most effective for NETs treatment (Kwekkeboom, *et al.*, 2006). Some alternative radionuclides (Table 1) can be considered for the treatment of NETs.

The growing number of studies indicates that various SSAs radiolabelled with ^{90}Y and ^{177}Lu have played an important role in NETs management strategy. For instance, ^{90}Y -octreotide and ^{177}Lu -octreotate demonstrated OR rates of 15–35% (Baum, *et al.*, 2015). Recent clinical studies indicated that PRRT can prolong the 5-year survival rate and improve quality of life factors in a considerable number of NETs patients. Moreover, PRRT achieved higher median 5-year survival compared to patients with untreated, conventional chemotherapy, transarterial chemoembolization (TACE) and transarterial embolization (TAE) (Bodei, *et al.*, 2014). In particular, ^{90}Y has demonstrated significant contribution in the treatment of NETs as well as liver tumor without causing extreme dose to neighboring healthy tissues (Fenwick, *et al.*, 2014). A study showed that therapy outcome of NETs using ^{90}Y -DOTA-TOC increased with adding of ^{131}I -MIBG (Bushnell, *et al.*, 2014).

In a more detailed study, it was shown that PRRT using ^{90}Y -DOTA-TATE and ^{90}Y -DOTA-TOC in patients with progressive metastatic NETs

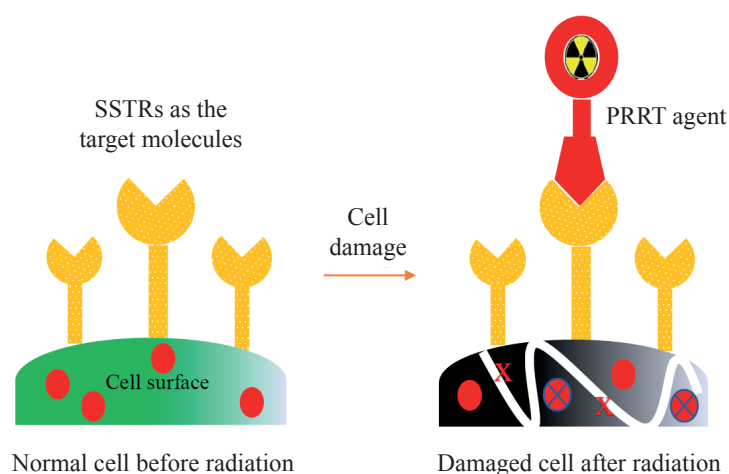


Figure 3. The schematic diagram illustrated the role of PRRT in the treatment of NETs.

Table 1. Alternative radionuclides for PRRT.

Radionuclide	Half-life ($T_{1/2}$)	Emissions	Reference
^{111}In	67.4 hours	γ , e^- Auger	(Dash, <i>et al.</i> , 2015)
^{67}Cu	61.9 hours	β^- , γ	(Dash, <i>et al.</i> , 2015)
^{47}Sc	82.1 hours	β^- , γ	(Dash, <i>et al.</i> , 2015)
^{161}Tb	165.6 hours	β^- , γ	(Dash, <i>et al.</i> , 2015)
^{225}Ac	240.0 hours	α , β^- , γ	(Dash, <i>et al.</i> , 2015)
^{213}Bi	0.77 hours	α , β^-	(Dash, <i>et al.</i> , 2015)
^{64}Cu	12.8 hours	β^- , β^+	(Cremonesi, <i>et al.</i> , 2006)
^{166}Ho	26.8 hours	β	(Cremonesi, <i>et al.</i> , 2006)
^{188}Re	17.0 hours	β^-	(Cremonesi, <i>et al.</i> , 2006)

were correlated with high values of positive response (24.5%) and stable disease (47%). Those values contributed to significant overall survival (OS) in patients. This study also revealed that renal toxicity was rare, however, the hematological toxicity was common (Vinjamuri, *et al.*, 2013). Another clinical study showed that a single cycle of 5 GBq ^{90}Y -DOTA-TATE was effective for treating metastatic NETs in the liver. Patient follow-up showed only single liver metastasis observed after 12 months of PRRT treatment (Baum, *et al.*, 2012).

The current study also showed that ^{177}Lu -octreotate highly effective for treating advanced NETs of the small intestine and demonstrated stable disease in 47.5% patients and only 8.2% patients indicated with progressive disease (Sabet, *et al.*, 2015). The positive contribution of ^{177}Lu -octreotate also reported by Ezziddin and co-workers with a median PFS and OS in advanced grade 1/2 pNETs were 34 and 53 months, respectively. Furthermore, the partial response, minor response, stable disease and progressive disease were observed in 60.3, 11.8, 13.2, and 14.7% patients, respectively (Ezziddin, *et al.*, 2014). Kwekkeboom, *et al.*, reported that a high value of stable disease of gastroenteropancreatic NETs (GEPNETs) was achieved by ^{177}Lu -DOTA-

TATE in 30 patients (40%) (Kwekkeboom, *et al.*, 2006). More recently, a study showed that longer OS was achieved in patients with bronchial NET or GEPNETs after PRRT with ^{177}Lu -DOTA-TATE compared to control group (van der Zwan, *et al.*, 2019).

The used of ^{90}Y and ^{177}Lu in combination formula showed more advantages than single treatment using ^{90}Y or ^{177}Lu . In the pre-clinical study using rats tumor model, remarkable antitumor activity was achieved by the combination of ^{90}Y -SSA and ^{177}Lu -SSA (50% : 50%) compared to single treatment using ^{90}Y -SSA or ^{177}Lu -SSA. This study also indicated that a combination of these radionuclides may become an effective strategy for eradication different size of tumor cells (de Jong, *et al.*, 2005). Kunikowska and colleagues reported that the combination of ^{90}Y and ^{177}Lu demonstrated longer OS in NETs patients than single radionuclide treatment. In this study, 25 patients were administered with ^{90}Y -DOTA-TATE (group A) and 25 patients were administered with the combination of $^{90}\text{Y}/^{177}\text{Lu}$ -DOTA-TATE (1 : 1) (group B). It was observed that the median event-free survival (EFS) in group A and B were 21.4 and 29.4 months, respectively. It also showed that 64% of patients from group

B experienced stable disease after 12 treatments, whereas only 52% from group A (Kunikowska, *et al.*, 2011). The comprehensive clinical study of PRRT in NETs treatment involving 27 patients has been reported by Matovic. This study used three different PRRTs: ^{90}Y -DOTA-TOC, ^{177}Lu -DOTA-TATE, and the combination of ^{90}Y -DOTA-TOC and ^{177}Lu -DOTA-TATE. It was concluded that the partial response, stable disease, and progressive disease were 25.9, 63.0, and 11.1%, respectively (Matovic, 2012).

The main challenge for developing PRRT is the appearance of side effects due to the radiation exposures which can affect the normal functions of several organs and tissues including kidney, blood, and bone marrow. Villard, *et al.*, reported that after a four cycles of therapy with ^{90}Y -DOTA-TOC, 15 patients (6.3%) experienced transient hematologic toxicities and 1 patient was diagnosed with acute myeloid leukemia. Interestingly, only 11 patients (4.4%) experienced severe transient hematologic toxicities and negative myeloproliferative was observed after radiotherapy using the combination of ^{90}Y -DOTA-TOC and ^{177}Lu -DOTA-TOC (Villard, *et al.*, 2012). To minimize the side effects, the role of excretion organs is crucial to accelerate the elimination of the radionuclide after the treatment. For example, the pathway involves reabsorption of the radionuclide by kidneys should be minimized. In order to overcome this issue, some organic compounds such as gelofucine and amino acids (*e.g.*, lysine and arginine) have been used to reduce radionuclide uptake by the kidney (Vinjamuri, *et al.*, 2013; Edgar, 2006).

Combined Therapy in NETs

The use of SSAs in routine clinical practice as an extensive treatment modality has revolutionized the management strategy of patients with NETs. In many patients, symptomatic relief and stabilization of tumor growth are achieved after the treatment using SSAs. However, partial or complete spontaneous tumor regression is considered a rare phenomenon, and therefore combined therapy

using SSA featuring other therapy strategies are crucial to further enhance the clinical achievement in NETs patients (Uri, *et al.*, 2018).

Currently, synergistic effects of combined therapy of SSA and PRRT (SSA-PRRT) have been reported. A retrospective observational study in 99 patients with G1/G2 NETs suggested that the median PFS for sequence therapy with SSA-chemotherapy was 20 months, while for SSA-PRRT was 30 months. Despite there was no statistical difference in PFS, those two sequence therapy provided higher PFS compared to SSA standard dose-SSA high dose (median PFS was not reached), but lower than SSA-everolimus (33 months). This study also showed that the number of side effects in patients was higher in SSA-everolimus and SSA-chemotherapy groups compared to SSA standard dose-SSA high dose and SSA to PRRT groups (Faggiano, *et al.*, 2019). Again, from a different retrospective observational study in 168 patients with GEPNETs, it was found that the median PFS for PRRT was 27 months in group I (PRRT monotherapy). Interestingly, the median PFS was increased to 48 months in group II when SSA was combined with PRRT (Yordanova, *et al.*, 2018).

Furthermore, combined therapy using chemotherapy and PRRT (chemo-PRRT) has become an interesting therapeutic option for patients with advanced or relatively aggressive behaving metastatic NETs, especially when it is unlikely to achieve favorable response to a single treatment strategy (Basu, *et al.*, 2016). The synergistic effect of combined PRRT using ^{177}Lu -DOTA-TATE with chemotherapeutics agents capecitabine + temozolomide (CAPTEM) was reported in 30 patients with inoperable G1/G2, progressive, functional or non-functional pNET. In this study, the median PFS was 48 months, while overall response rate (ORR) and disease control rate (DCR) were 80% and 100%, respectively (Ramage, *et al.*, 2018). These results suggest that combined therapy using chemo-PRRT is likely to increase the PFS in patients rather than single treatment with chemotherapy or PRRT alone. Moreover, *in vivo* study in mice bearing SSTR-ex-

pressing H69 demonstrated that chemo-PRRT using TMZ and ^{177}Lu -octreotate resulted in tumor size reduction.

Despite chemo-PRRT has shown encouraging results, negative interactions between the two treatments should be taken into consideration. For instance, chemotherapy agents might influence the SSTR-2 (PRRT target) expression on tumor cells. Additionally, tumor vasculature might be affected by chemotherapy whereas adequate tumor perfusion is required for local biodistribution and accumulation of PRRT agent (Bison, *et al.*, 2015). Furthermore, in a study by Brieau, *et al.*, a high occurrence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in GEPNETs patients treated with PRRT after previous chemotherapy with alkylating agents were observed. This study suggests that the importance of previous chemotherapy before PRRT should be considered (Brieau, *et al.*, 2016).

CONCLUSION

The management of NETs poses a serious challenge due to the heterogeneous clinical presentations and varying degree of aggressiveness. Therefore, the application of a combined treatment using two or more strategies may become a better option. More importantly, the treatment approach for NETs patients should be individualized based on each tumor characteristics. Over the last few years, some advanced managements strategies have been explored, including the treatment using SSAs. More recently, SSAs have also been used in PRRT strategy, especially for the treatment of inoperable or metastasized NETs. These strategies play an important role and have been proved as advanced techniques for treating NETs. Moreover, treatment using the combination of SSAs and PRRT or chemotherapy and PRRT showed encouraging outcome for the patients as compared with single treatment either using SSAs, chemotherapy or PRRT alone. As a result, NETs management based on SSAs has increased and likely to become a continuing trend

in routine clinical practice. More in-depth study, however, is needed to further understanding the role of SSAs in the treatment of NETs.

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