Review Article

Developmental Trends in Targeted Radionuclide Therapy of Neuroendocrine Tumors

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ABSTRACT

Neuroendocrine tumors (NETs) constitute a heterogeneous group of neoplasms including carcinoids, pancreatic neuroendocrine tumors, pituitary tumors, medullary thyroid carcinoma and phaeochromocytomas. The symptoms and the outcome of NETs differ considerably between patients depending on several factors. By labelling tracers with a radioisotope, the tracer acts as a carrier to deliver the radioactivity to tissues expressing somatostatin receptors (SSTRs) and may be used for diagnosis and treatment. Several factors influence the selection of an appropriate therapeutic radioisotope. A longer physical half-life and low dose rate may be more effective for relatively indolent malignancies such as NETs. Radiolabelled targeted therapy is a fairly recent and promising modality for the management of patients with inoperable or disseminated NETs when conventional therapies fail.

Key Words: Neuroendocrine tumors, Somatostatin receptors, Targeted therapy

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INTRODUCTION

Neuroendocrine tumors (NETs) constitute a heterogeneous group of neoplasms including carcinoids, pancreatic neuroendocrine tumors, pituitary tumors, medullary thyroid carcinoma and phaeochromocytomas. The definition of neuroendocrine cells refers to cells with neurotransmitter, neuromodulator or neuropeptide hormone production, dense-core secretory granules, and the absence of axons and synapses (1). Thus, they have features common with neurons containing secretory granulae and with endocrine cells because peptides are released by exocytosis upon stimulation of the cells. The symptoms and the outcome of NETs differ considerably between patients depending on several factors. The so called functional tumors give rise to symptoms related to the effect of hormonal overproduction for instance flush, diarrhea, bronchconstriction, hypoglycaemia, whereas the non-functioning tumors may cause local symptoms related to tumor size. The hormonal production from carcinoid liver metastases may lead the patient to the doctor because of carcinoid heart disease affecting the valves on the right side. The slow growing NETs have a more benign course than the highly proliferating clinically aggressive tumors. The only curative treatment is surgery and is the therapeutic choice in the case of localised disease or with occasional metastases limited to lymph nodes and/or the liver. For treatment of a limited number liver metastases, surgical resection and/or radiofrequency ablation (RFA) of <3 to 4 cm may be performed whereas more extensive disease is treated by non-surgical methods.

NET cells commonly express somatostatin receptors (SSTRs) in their cell membrane and somatostatin inhibits the secretion and action of a number of peptide hormones, neurotransmitters, and exocrine secretions of the GEP axis and may control cell proliferation in normal tissues and in tumors. The development of potent, long-acting somatostatin analogues with a half-life of over 100 minutes was therefore a breakthrough for clinical application (2). Somatostatin analogue therapy delivered as either a subcutaneous or intravenous injection is usually effective in relieving hormonal symptoms. Moreover, Interferon may also be considered for symptom control in some patients (3).

For tumor staging, morphological imaging by computed tomography (CT) is performed together with functional imaging by somatostatin receptor scintigraphy (SRS). Usually octreotide is labelled with ^{111}In using a chelate to form ^{111}In-DTPA-octreotide, which is available as a commercial product (OctreoScan®). Patients with extensive and progressive liver metastases are conventionally treated by intraarterial embolisation, based on the fact that the normal liver parenchyma is supplied with blood by the portal vein (about 75%) whereas the tumors rely on the liver artery. Symptomatic bone metastases are generally subjected to external radiation therapy.

Targeted radionuclide therapy yields a higher absorbed radiation dose to the tumor comparing with external radiation therapy which is important for relatively radio-resistant NETs compared with other solid tumors (4). Targeted tumor localisation allows treatment to be administered systemically which is an effective option for patients with inoperable or disseminated disease.

Concept of radio-targeted therapy

Targeted radionuclide therapy has derived from diagnostic radionuclide imaging i.e. SRS which take advantages of the over-expression of SSTRs on the cell surfaces of a range of NETs (4). Several of these receptors, including SSTR sub types 2 and 5, are important to inhibit gastrointestinal and pancreatic hormone secretion and SSTR-1 is thought to mediate cell-cycle arrest and apoptosis (5). By labelling octreotide with a radioisotope, the octreotide acts as a carrier to deliver the radioactivity to tissues expressing SSTRs and may be

used for diagnosis and treatment. Initially, ^{111}In-octreotide (OctreoScan) was used both for localisation and treatment of NETs but for therapy ^{111}In has now been replaced by other radioisotopes with different physical properties.

Radionuclide selection

Several factors influence the selection of an appropriate therapeutic radioisotope. It is important that the physical half-life of the radionuclide matches the biological turnover of the tracer in vivo. A high dose rate is more suitable for rapidly dividing tumors. A longer physical half-life and low dose rate may be more effective for relatively indolent malignancies such as NETs. The main target to cause cell death is the nucleus. Usually, beta emitters are utilised and the selected radionuclide must therefore have an appropriate path length to reach the nucleus, depending on the site of cellular radiopharmaceutical concentration. Metaiodobenzylguanidine (MIBG) is a guanethidine analogue which is selectively concentrated by the neuroadrenergic system and by tumors of neuroectodermal origin, including phaeochromocytomas, carcinoid tumors and medullary thyroid carcinoma (4). [^{131}I]MIBG is stored in cytoplasmic vesicles, and therefore the nucleus is located well within the range of medium energy beta particles from ^{131}I. Tracers which target the cell surface, such as somatostatin analogues, require a longer beta particle range to reach the nucleus and it is better to label with high energy beta emitters such as ^{90}Y or ^{170}Lu. Furthermore, the tumor uptake is generally heterogenous due to poor tumor vascularity, high interstitial pressure and subsequent central necrosis in large tumors (4).This heterogeneous uptake, highlights the role of particle range and energy to target the untargeted malignant cells by cross-fire effects. Direct intra-arterial injection achieves higher intra-tumoral concentrations of the radiotracer and may be of value in treating isolated hepatic or cerebral lesions, but is less helpful in managing disseminated disease (4).

Treatment evaluation

Responses to therapy must be assessed by uniform criteria and divided into symptomatic, hormonal and tumor responses (6). Tumor responses are classified by WHO criteria including:

1. *Complete response*, complete regression of all clinical and hormonal evidence of tumor, including radiological abnormalities.
2. *Partial response*, a 50% or greater reduction of all measurable tumor and no appearance of new lesions, along with hormonal and symptomatic improvement.
3. *Stable disease*, a less than 50% reduction or no greater than 25% increase of tumor size, hormonal measurements and symptoms
4. *Progression*, appearance of new lesions or an increase of 25% or more of tumor size, and hormonal and symptomatic deterioration.

TARGETED RADIOTHERAPIES

[^{131}I]MIBG

A survey of the MIBG practice in Europe was undertaken in 1999 (4). Data were collated from 14 institutions undertaking [^{131}I]MIBG therapy of a range of NETs. Pancreatic NETs are rarely MIBG avid and were not included in the survey. Over 99% of 537 treated patients had refractory, stage III/IV disease. When childhood neuroblastoma was excluded, the overall objective response (complete and partial tumor response) was 30%. This was associated with reduction of measurable tumor markers (complete and partial response) in 38% of patients and subjective response in 52%. Toxicity was virtually confined to temporary myelosuppression – 14% World Health Organization grades I and II; 3% grades III and IV. Mean response duration was 18.4 months (range 1-144 months). The combination of high symptom benefit with low toxicity suggests that

[^{131}I]MIBG therapy is a valuable palliative treatment option for patients with advanced NETs. Preliminary data suggest a relationship between the amount of injected radioactivity and the treatment response with better response at higher cumulative administered radioactivity, but formal phase II studies are required to investigate this further.

Radiolabelled SSTR analogues

A large number of NETs, mainly gastroenteropancreatic (GEP) NETs (functioning or non-functioning), are being treated with SSTR analogues. This is particularly important, to relieve sometimes severe hormonal symptoms for which continuous treatment with SSTR analogues is required (6). Before treatment with unlabelled and radiolabelled somatostatin analogues is initiated, the patients' eligibility for this therapy is tested by ^{111}In-octreotide (OctreoScan). Localization of SSTR expressing NETs with an uptake of ^{111}In-octreotide is similar to or higher than that of the liver is required. The administration of high doses of the Auger electron and γ-emitter ^{111}In-diethylenetriaminepenta-acetic acid (DTPA) octreotide in patients with metastatic tumors has been associated with considerable symptomatic improvement but relatively few and short-lived objective tumor responses (6). The use of ^{90}Y, a pure beta emitter, in ^{90}Y-1,4,7,10 tetraazacyclododecane-N,N0,N00,N000-tetraacetic acid (DOTA) Tyr3 octreotide (^{90}Y-DOTATOC), has been associated with 10–30% objective tumor response rates, and appears to be particularly effective in larger tumors (6). ^{111}In- and ^{90}Y-DOTA-lanreotide has also been used for the treatment of NETs although its therapeutic efficacy is probably inferior to that of octreotide-based radiopharmaceuticals (6). Also, in a clinical trial study, hepatic intraarterial injection of ^{90}Y-DOTA-lanreotide resulted in safe and effective palliative treatment for patients with progressive large-volume somatostatin receptor–positive liver metastases (7).

Treatment with ^{177}Lu-DOTA Tyr3 octreotate (^{177}Lu-DOTATATE), which has a higher affinity for the SSTR subtype 2, has resulted in approximately 30% complete or partial tumor response showing particularly effect on smaller tumors (6). Also, treatment with ^{177}Lu-octreotate has resulted in tumor remission in a high percentage of patients with GEP tumors with rare serious side effects and favourable median time to progression compared with chemotherapy (8). Paragangliomas and meningiomas (somatostatin receptor expressing non-GEP tumors) can be treated by ^{177}Lu-Octreotate, but the response rates are lower than those in patients with GEP NETs (9). ^{177}Lu-octreotate treatment can also be effective in patients with bronchial and gastric carcinoids but its role in thymic carcinoids cannot be determined yet because of the limited number of patients (10).

Furthermore, treatment using both ^{90}Y-DOTATOC and ^{177}Lu-DOTA Tyr3 octreotate seems promising, as the combination of these radiopharmaceuticals could be effective in patients with a mixture of small and large lesions (6).

It is not only beta emitters that are used in treatment of NETs. In a study, DOTATOC labelled with the high linear energy transfer (LET) alpha-emitter, ^{213}Bi showed dose-related anti-tumor effects with minimal treatment related organ toxicity (mild, acute nephrotoxicity) and maintained ^{213}Bi-DOTATOC a promising therapeutic radiopharmaceutical for further evaluation (11). Tumor regression is positively correlated with a high level of uptake at SRS, limited tumor mass and good performance status and in general, better responses have been obtained in GEP NETs than in other NETs (6).

The side effects of this form of therapy are relatively few and mild, particularly when kidney-protective agents are used and targeting therapy with radiolabelled

somatostatin analogues is a promising treatment option for patients with inoperable or disseminated NETs. (12).

However, imaging and targeted radionuclide therapy using radiolabelled somatostatin analogues play an important role in molecular imaging and management of NETs. Balancing of advantages, i.e. clinical response to radionuclide therapy and disadvantages such as normal organ radio-toxicity are important and careful assessment of biodistribution, dosimetry, and toxicity must be done individually. Improvements in this field can be expected from new compounds with higher or broader receptor affinity, induction of increased receptor expression on tumor cells, and the use of radioisotopes combination therapy (13).

CONCLUSION

In NET patients, surgery is the first therapeutic option in localised disease and can be supplemented by RFA of a small number of ≤ 3-4 cm liver metastases. Symptoms generally are relieved by subcutaneous or intramuscular somatostatin analogue therapy that also may exhibit an antiproliferative effect. More extended disease in the liver is generally treated by intraarterial embolisation. Radiolabelled targeted therapy is a fairly recent and promising modality for the management of patients with inoperable or disseminated NETs when conventional therapies fail. In order to obtain optimal results it is important to select the most suitable compound with high affinity, labelled with an appropriate therapeutic radioisotope and to carefully and for the individual patient assess biodistribution, dosimetry, and toxicity. Treatment with ^{111}In-, ^{90}Y- or ^{177}Lu-labelled SS analogues has been associated with considerable symptomatic improvement with limited side effects. Targeted therapies are better tolerated than other systemic treatments (6) and deliver higher absorbed radiation doses to the tumor compared with external radiation therapy (4, 6). [^{90}Y-DOTA0,Tyr3]-octreotide and [^{177}Lu-DOTA0,Tyr3]-octreotate have resulted in substantial tumor regression when used as single agents but a combination of these two compounds may be even more effective (6).

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