



Evidence-Based Series 12-13

Radionuclide Therapy for Neuroendocrine Malignancies

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and members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel*

A Quality Initiative of the
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Evidence-Based Series 12-13: Section 1

**Radionuclide Therapy for Neuroendocrine Malignancies:
Guideline Recommendations**

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QUESTIONS

1. What are the effects of the eight commonly used and studied therapeutic radiopharmaceuticals described in Table 1 below in patients with different types of neuroendocrine malignancies?
2. Which one of the eight therapeutic radiopharmaceuticals is most effective in improving clinical outcomes (i.e., tumour response, duration of tumour response, overall survival [OS] time/rate, progression-free survival [PFS] time/rate, biochemical response, and quality of life [QOL]) in the above patients?
3. What are the toxicities for each therapeutic radiopharmaceutical?

Table 1. Radiopharmaceuticals considered by this practice guideline.

Name	Alternate name
¹¹¹ In-DTPAOC	[¹¹¹ In-DTPA ⁰]octreotide, ¹¹¹ In-DTPA-D-Phe-octreotide, ¹¹¹ In-pentetreotide
¹¹¹ In-DOTATATE	¹¹¹ In -DOTA-TYR ³ -octreotate, ¹¹¹ In-octreotate
⁹⁰ Y-DOTATOC	⁹⁰ Y-DOTA-TYR ³ -octreotide, ⁹⁰ Y-SMT487, ⁹⁰ Y-edotreotide
⁹⁰ Y-DOTALAN	⁹⁰ Y-DOTA-lanreotide
⁹⁰ Y-DOTATATE	⁹⁰ Y-DOTA-TYR ³ -octreotate, ⁹⁰ Y-octreotate
¹⁷⁷ Lu-DOTATOC	¹⁷⁷ Lu-DOTA-TYR ³ -octreotide, ¹⁷⁷ Lu-octreotide
¹⁷⁷ Lu-DOTATATE	¹⁷⁷ Lu-DOTA-TYR ³ -octreotate, ¹⁷⁷ Lu-octreotate
¹³¹ I-MIBG	¹³¹ I-metaiodobenzylguanidine, ¹³¹ I-iobenguane

TARGET POPULATION

These recommendations apply to neuroendocrine cancer patients who are inoperable, or have residual disease following surgery or other ablative therapy, or have metastases.

INTENDED USERS

This guideline is intended for nuclear medicine physicians, medical oncologists, surgeons, and pathologists who are involved in the treatment of the above-targeted patients.

INTRODUCTION

Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms: they include epithelial neuroendocrine carcinomas originating in multiple sites throughout the body as well as tumours of modified neurons arising in sympathetic or parasympathetic ganglia and the adrenal medulla (1,2). The latter express tyrosine hydroxylase to synthesize dopamine and, therefore, readily take up ^{131}I - and ^{123}I -MIBG; however, the former express somatostatin receptors as a distinguishing feature and are amenable to ablation with radiolabeled somatostatin analogues (1,2). Although therapy with both MIBG and radiolabeled somatostatin analogues has been provided in Ontario, it has not been made broadly available: barriers to access have resulted in out-of-country requests. A systematic review was conducted to inform the recommendations for the selection of agents for therapy and to inform the development of criteria for access to radionuclide therapies for NET patients in Ontario. The details of the method and results of this systematic review are shown in Section 2. There are no randomized controlled trials (RCTs) examining the effectiveness of any of the peptide receptor radionuclide therapy (PRRT) agents or ^{131}I -MIBG in the treatment of neuroendocrine cancer patients. Trials have not been conducted to compare either PRRT or ^{131}I -MIBG with placebo, systemic therapy, tumour debulking treatment, or long-acting somatostatin analogues. Furthermore, no trials have been conducted to make direct comparisons between or among the eight agents reviewed.

RECOMMENDATIONS AND KEY EVIDENCE

The Expert Panel and the Working Group offer the following recommendations based on the evidence reviewed:

- PRRT appears to be an acceptable option in adult patients with neuroendocrine cancer who are inoperable, have residual disease following surgery or other ablative therapy, or have metastases. PRRT is relatively safe and well tolerated with renal protection using lysine and arginine amino acid solution, especially for ^{90}Y -DOTALAN and ^{177}Lu -DOTATATE. However, renal function must be monitored.
- Treatment with PRRT in Ontario should be conducted as part of one or more RCTs, or in large comparative clinical trials if an RCT is not feasible, under the authority of a Clinical Trials Agreement, to clarify the further effects of PRRT (for example, comparing ^{177}Lu -DOTATATE with sunitinib in an RCT).
- ^{131}I -MIBG may be effective for malignant neuroblastoma, paraganglioma, or pheochromocytoma, but there is insufficient evidence to suggest its efficacy for adult neuroendocrine carcinoma patients. However, the hematologic toxicity, severe infections, and secondary malignancies possible afterwards should be considered.

Qualifying Statements

- There is limited evidence, based on a historical comparison of studies from a single centre (see Key Evidence below), that ^{177}Lu -DOTATATE may be associated with greater OS, PFS, and overall response rate (defined as the sum of complete response, partial response, and minor response rates) compared with ^{90}Y -DOTATOC or ^{111}In -DTPAOC. Therefore, ^{177}Lu -DOTATATE would be an appropriate agent to include in the future clinical trials described above.

- Prior to the administration of therapy, the tumours from NET patients who are to receive PRRT or ¹³¹I-MIBG should demonstrate a positive uptake of the related diagnostic agent.
- A recommendation cannot be made for or against the use of PRRT in early-stage NET patients, as there is no relevant evidence.

Key Evidence

Peptide Receptor Radionuclide Therapy

- Fifteen prospective single-arm articles (3-17) and one prospective comparative study (18) met the study selection criteria; of the nine published after 2005, all investigated the effects of ⁹⁰Y-DOTATOC, ⁹⁰Y-DOTATATE, or ¹⁷⁷Lu-DOTATATE (9-17). The total sample size was 1179. All the patient tumours showed a higher or the same uptake on octreoscan than on liver uptake before PRRT. All but one study (12) reported the overall response rate as determined by three different imaging criteria in a variety of stage III-IV NET subgroups. Across all agents, overall response rates ranged from 5% to 75% in various tumour subgroups, with wide 95% confidence intervals (CI) (See Figure 2 in Section 2).
- Three studies were conducted in the same clinical centre to investigate the effects of ¹¹¹In-DTPAOC, ⁹⁰Y-DOTATOC, and ¹⁷⁷Lu-DOTATATE at different time periods (5,10,13). The median OS and PFS time was 37 and 14 months, respectively, for ⁹⁰Y-DOTATOC at five-year follow-up (10), and 46 and 33 months, respectively, for ¹⁷⁷Lu-DOTATATE at four years (14). The overall response rate was 18% (CI, 6% to 30%) for patients with progressive stage III-IV NET treated with ¹¹¹In-DTPAOC, 21% (CI, 11% to 31%) for patients with stage III-IV neuroendocrine gastroenteropancreatic tumours (GEP-NET) treated with ⁹⁰Y-DOTATOC, and 46% (CI, 40% to 52%) for patients with stage IV GEP-NET disease treated with ¹⁷⁷Lu-DOTATATE.
- Eight of the 16 articles reported survival outcomes, with six reporting median OS times ranging from 15 to 46 months for various stage III-IV NET subgroups (10,11,13,15-17). There was no significant difference in OS time between the intervention (14 patients treated with ¹¹¹In-DTPAOC and five patients treated with ¹³¹I-MIBG) and control arm in the unique comparative trial (18).
- Of the fifteen articles that reported on toxicity, 11 specified one of two criteria used for grading toxicity. Nausea and vomiting were common during therapy. The severe toxicities included the following: for ¹¹¹In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (5); for ⁹⁰Y-DOTATOC, 0.9% to 3.4% of patients developed grade 4 renal toxicity in three studies (9-11), with 2% of patients developing MDS in one study (10); for ⁹⁰Y-DOTALAN, no severe toxicity was found in one study (6); for ⁹⁰Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (16); and for ¹⁷⁷Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% developed MDS, and 0.4% developed renal insufficiency in one study (13). For studies investigating the effects of ⁹⁰Y-DOTATOC, ⁹⁰Y-DOTATATE, and ¹⁷⁷Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function.

¹³¹I-MIBG Therapy

- Six prospective single-arm, one retrospective comparative, and one retrospective single-arm study examining the effectiveness of ¹³¹I-MIBG were eligible; the total sample size was 612. All the patients showed at least one lesion as positive on the ¹²³I-MIBG or ¹³¹I-MIBG scintigraphy. The overall tumour response rate on imaging by various imaging criteria ranged from 32% to 75% for stage III-IV pediatric neuroblastoma patients with a median age of 2.0 to 6.6 years old (19-23) and was 26% for adult and stage III-IV NET patients (24) (including 22 neuroblastomas, 10 pheochromocytomas, three paragangliomas, six medullary thyroid carcinomas, and four carcinoids) and 27% for

patients with stage IV paraganglioma or pheochromocytoma (25) (See Figure 3 in Section 2).

- The Sywak et al study was the unique comparative study for comparing standard therapies alone with standard therapies plus ¹³¹I-MIBG in stage IV patients with midgut carcinoid (26). The OS rate was 63% (CI, 47% to 75%) in the intervention group and 47% (CI, 34% to 59%) in the control group at five years, without statistical significance (p=0.10).
- Of seven studies reporting on toxicity, three used different criteria, and four studies did not specify the criteria for toxicity grading. Hematologic toxicities were the main severe side effects. Forty-three percent of patients had bone marrow replacement (BMR), and one patient developed secondary leukemia in one study (19). Five percent of patients in one study (20) and 2% of patients in another study (22) developed leukemia or MDS. In a retrospective study, five (4%) three- to five-year-old neuroblastoma patients developed secondary malignancies after ¹³¹I-MIBG therapy either as part of first-line therapy or as salvage therapy for resistant or recurrent disease: one acute nonlymphoblastic leukemia at one and a half years, one chronic myelomonocytic leukemia at four years, one malignant schwannoma at seven years, one rhabdomyosarcoma at 14 years, and one angiomatoid malignant fibrous histiocytoma at 10 years after ¹³¹I-MIBG (21). In a fifth study, 39% of patients needed autologous BMR, and 9% of patients died (23) where ¹³¹I-MIBG was utilized as the first-line treatment. Forty-one percent of patients had grade 2-3 hematologic toxicities in a sixth study (24). After an accumulative dose of at least 63.3 gigabecquerels (GBq) ¹³¹I-MIBG therapy, 4% of patients who did not have prior radiation or chemotherapy developed MDS and acute myeloid leukemia at two and five years, respectively, in the seventh study (25). In addition, 4% of patients in that same study developed acute respiratory distress syndrome, 4% developed bronchiolitis obliterans organizing pneumonia, and 2% had a pulmonary embolism.

Treatment Alternatives

An RCT has shown somatostatin analogs to be more effective than placebo in the control of tumour growth in patients with metastatic midgut NETs (27).

Recently, investigators of two studies have reported positive results in the use of biologic agents for the treatment of malignant pancreatic NETs: one was the tyrosine kinase inhibitor sunitinib, and the other was the mTOR (mammalian target of rapamycin) inhibitor, everolimus (28,29). Both trials were phase III, multicentre, double-blind, randomized, placebo-controlled trials with sufficient numbers of patients to yield clear statistical results. Sunitinib, as compared with placebo, caused more than a doubling in PFS (11.4 versus [vs.] 5.5 months, respectively, p<0.001). Everolimus caused a 65% reduction in the estimated risk of progression (PFS of 11.0 months for everolimus vs. 4.6 months for placebo, p<0.001).

FUTURE RESEARCH

The recent publications that report positive results with the biological agents of sunitinib, everolimus, and octreotide long-acting release (LAR), particularly with regard to PRRT, raise many important questions that could be the subject of further investigation. Should these drugs be used before, after, or in combination with PRRT? Can these drugs be used alone or in combination with PRRT as adjuvant or neoadjuvant therapy (with surgery)? For malignant NET patients with negative uptake on octreoscan or renal insufficiency and positive uptake on ¹²³I-MIBG scintigraphy, does ¹³¹I-MIBG work well? Furthermore, the use of PRRT early in the treatment of NET patients (i.e., before maximal medical treatment) has not been explored and should be an option for further study in Ontario.

The development of a standardized program for the assessment, treatment, and follow-up of NET patients in Ontario is essential to ensure the existence of an appropriate infrastructure for the evaluation of promising new therapies that would provide patients suffering from NETs with high-quality, evidence-based care.

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