Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 12-13

Radionuclide Therapy for Neuroendocrine Malignancies

K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law,
and members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 15, 2011

An assessment conducted in January 2022 deferred the review of Evidence-based Series (EBS) 12-13. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 12-13 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1356

Section 1: Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

For further information about this series, please contact:

Dr. Karen Y. Gulenchyn, Clinical Associate Professor Radiology & Medicine, McMaster University
Chief of the Department of Nuclear Medicine
Hamilton Health Sciences & St. Joseph's Healthcare Hamilton
Hamilton Health Sciences, 1200 Main Street West, HSC-1P15, Hamilton, ON, L8N 3Z5
Phone: 905-521-2100 ext. 75667 Fax: 905-546-1125 E-mail: gulenkar@hhsc.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775

PEBC Report Citation (Vancouver Style): Gulenchyn KY, Yao X, Asa SL, Singh S, Law C. Radionuclide therapy for neuroendocrine malignancies. Toronto (ON): Cancer Care Ontario; 2011 Aug 15. Program in Evidence-based Care Evidence-Based Series No.: 12-13.

Journal Citation (Vancouver Style): Gulenchyn KY, Yao X, Asa SL, Singh S, Law C. Radionuclide therapy in neuroendocrine tumours: a systematic review. Clin Oncol (R Coll Radiol). 2012 May;24(4):294-308.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 12-13: Section 1

Radionuclide Therapy for Neuroendocrine Malignancies: Guideline Recommendations

K.Y. Gulenchyn, X. Yao, S.L. Asa, S. Singh, C. Law,
and members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 15, 2011

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 ^{131}I-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 ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, or ^{177}Lu-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 ^{111}In-DTPAOC, ^{90}Y-DOTATOC, and ^{177}Lu-DOTATATE at different time periods (5,10,13). The median OS and PFS time was 37 and 14 months, respectively, for ^{90}Y-DOTATOC at five-year follow-up (10), and 46 and 33 months, respectively, for ^{177}Lu-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 ^{111}In-DTPAOC, 21% (CI, 11% to 31%) for patients with stage III-IV neuroendocrine gastroenteropancreatic tumours (GEP-NET) treated with ^{90}Y-DOTATOC, and 46% (CI, 40% to 52%) for patients with stage IV GEP-NET disease treated with ^{177}Lu-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 ^{111}In-DTPAOC and five patients treated with ^{131}I-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 ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (5); for ^{90}Y-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 ^{90}Y-DOTALAN, no severe toxicity was found in one study (6); for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (16); and for ^{177}Lu-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 ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function.

^{131}I-MIBG Therapy

- Six prospective single-arm, one retrospective comparative, and one retrospective single-arm study examining the effectiveness of ^{131}I-MIBG were eligible; the total sample size was 612. All the patients showed at least one lesion as positive on the ^{123}I-MIBG or ^{131}I-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 ^{131}I-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 ^{131}I-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 ^{131}I-MIBG (21). In a fifth study, 39% of patients needed autologous BMR, and 9% of patients died (23) where ^{131}I-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) ^{131}I-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-active 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 ^{123}I-MIBG scintigraphy, does ^{131}I-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.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Contact Information

For further information about this report, please contact:
Dr. Karen Y. Gulenchyn, Clinical Associate Professor Radiology & Medicine, McMaster University
Chief of the Department of Nuclear Medicine Hamilton Health Sciences
& St. Joseph's Healthcare Hamilton
Hamilton Health Sciences, 1200 Main Street West, H S C-1P15, Hamilton ON L8N 3Z5
Phone: 905-521-2100 ext. 75667 Fax: 905-546-1125 E-mail: gulenkar@hhsc.ca

For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/
or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775

REFERENCES

1. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and genetics of tumours of endocrine organs. Lyon, France: IARC Press; 2004.
2. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumours: the WHO classification. Ann NY Acad Sci. 2004;1014:13-27.
3. Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol. 2001;12:941-5.
4. Paganelli G, Bodei L, Handkiewicz Junak D, Rocca P, Papi S, Lopera Sierra M, et al. 90Y-DOTA-D-Phe1-Try3-octreotide in therapy of neuroendocrine malignancies. Biopolymers. 2002;66:393-8.
5. Valkema R, De Jong M, Bakker WH, Breeman WA, Kooij PP, Lugtenburg PJ, et al. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. Semin Nucl Med. 2002;32:110-22.
6. Virgolini I, Britton K, Buscombe J, Moncayo R, Paganelli G, Riva P. In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. Semin Nucl Med. 2002;32:148-55.
7. Waldherr C, Pless M, Maecke HR, Schumacher T, Crazzolara A, Nitzsche EU, et al. Tumour response and clinical benefit in neuroendocrine tumours after 7.4 GBq (90)Y-DOTATOC. J Nucl Med. 2002;43:610-6.
8. Teunissen JJ, Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumours treated with [177Lu-DOTA0,Tyr3]octreotate. J Clin Oncol. 2004;22:2724-9.
9. Forrer F, Waldherr C, Maecke HR, Mueller-Brand J. Targeted radionuclide therapy with 90Y-DOTATOC in patients with neuroendocrine tumours. Anticancer Res. 2006;26:703-7.
10. Valkema R, Pauwels S, Kvols LK, Barone R, Jamar F, Bakker WH, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumours. Semin Nucl Med. 2006;36:147-56.
11. Iten F, Muller B, Schindler C, Rochlitz C, Oertli D, Macke HR, et al. Response to [90Yttrium-DOTA]-TOC treatment is associated with long-term survival benefit in metastasized medullary thyroid cancer: a phase II clinical trial. Clin Cancer Res. 2007;13:6696-702.
12. Hubalewska-Dydejczyk A, Jurczak W, Sowa-Staszczak A, Kunikowska J, Królicki L, Gilis-Januszewska A, et al. New forms of radionuclide therapy with (90)Y in oncology. Nucl Med Rev. 2008;11:5-11.
13. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3] octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008;26:2124-30.
14. Teunissen JJM, Krenning EP, De Jong FH, De Rijke YB, Feelders RA, Van Aken MO, et al. Effects of therapy with [177Lu-DOTA0,Tyr 3]octreotate on endocrine function. Eur J Nucl Med Mol Imaging. 2009;36:1758-66.
15. Bushnell Jr DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol. 2010;28:1652-9.
16. Cwikla JB, Sankowski A, Seklecka N, Buscombe JR, Nasierowska-Guttmejer A, Jeziorski KG, et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol. 2010;21:787-94.

17. van Essen M, Krenning EP, Kam BLR, De Herder WW, Feelders RA, Kwekkeboom DJ. Salvage therapy with177Lu-octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. J Nucl Med. 2010;51:383-90.
18. Nguyen C, Faraggi M, Giraudet AL, de Labriolle-Vaylet C, Aparicio T, Rouzet F, et al. Long-term efficacy of radionuclide therapy in patients with disseminated neuroendocrine tumours uncontrolled by conventional therapy. J Nucl Med. 2004;45:1660-8.
19. Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, et al. Phase I dose escalation of 131I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol. 1998;16:229-36.
20. Garaventa A, Bellagamba O, Lo Piccolo MS, Milanaccio C, Lanino E, Bertolazzi L, et al. 131I-metaiodobenzylguanidine (131I-MIBG) therapy for residual neuroblastoma: a mono-institutional experience with 43 patients. Br J Cancer. 1999;81:1378-84.
21. Garaventa A, Gambini C, Villavecchia G, Di Cataldo A, Bertolazzi L, Pizzitola MR, et al. Second malignancies in children with neuroblastoma after combined treatment with 131I-metaiodobenzylguanidine. Cancer. 2003;97:1332-8.
22. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng SC, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol. 2007;25:1054-60.
23. de Kraker J, Hoefnagel KA, Verschuur AC, van Eck B, van Santen HM, Caron HN. Iodine-131-metaiodobenzylguanidine as initial induction therapy in stage 4 neuroblastoma patients over 1 year of age. Eur J Cancer. 2008;44:551-6.
24. Castellani MR, Chiti A, Seregni E, Bombardieri E. Role of 131I-metaiodobenzylguanidine (MIBG) in the treatment of neuroendocrine tumours. Experience of the National Cancer Institute of Milan. Q J Nucl Med. 2000;44:77-87.
25. Gonias S, Goldsby R, Matthay KK, Hawkins R, Price D, Huberty J, et al. Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. J Clin Oncol. 2009;27:4162-8.
26. Sywak MS, Pasieka JL, McEwan A, Kline G, Rorstad O. 131I-meta-iodobenzylguanidine in the management of metastatic midgut carcinoid tumours. World J Surg. 2004;28:1157-62.
27. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-63.
28. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumours. N Engl J Med. 2011;364:501-13.
29. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumours. N Engl J Med. 2011;364:514-23.