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PRACTICE GUIDELINE

Systemic therapy in incurable gastroenteropancreatic neuroendocrine tumours: a clinical practice guideline

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ABSTRACT

Purpose The purpose of the present review was to determine which antineoplastic systemic therapy is most effective in improving clinical outcomes for patients with incurable gastroenteropancreatic neuroendocrine tumours (NETs).

Methods A systematic search (2008–2016) of the literature in the MEDLINE and EMBASE databases and the Cochrane Database of Systematic Reviews was conducted; abstracts from the American Society of Clinical Oncology, the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the European Society for Medical Oncology, the European Cancer Congress, the European Neuroendocrine Tumor Society, and the North American Neuroendocrine Tumor Society were reviewed. Draft recommendations were created, and a comprehensive review process was undertaken. Outcomes—including progression-free survival (PFS), overall survival, objective response rate, adverse events, and quality of life—were extracted from each of the studies.

Results Eleven randomized controlled trials (RCTs), sixteen nonrandomized prospective studies, and thirteen retrospective studies met the inclusion criteria.

Conclusions Patients with well- or moderately-differentiated pancreatic NETs (PNETs) should receive targeted therapy (that is, everolimus or sunitinib), and patients with non-PNETs should be offered either targeted therapy (that is, everolimus) or somatostatin analogues (SSAs—that is, octreotide long-acting release or lanreotide). Evidence from two phase III trials demonstrated a significant PFS benefit for patients with PNETs. For patients with non-PNETs, the evidence comes from subgroup analyses of RCTs, as well as from a planned interim analysis. Although the evidence has limitations, the rarity of the disease, coupled with the difficulty of conducting methodologically sound trials in the affected population, means that treatment decisions have to make use of the best available evidence. Because of insufficient evidence for both PNETs and non-PNETs, no evidence-based recommendation can be made for or against other types of targeted therapy, other SSAs, chemotherapy, or combination therapy.

Key Words Systematic therapy, neuroendocrine tumours, gastroenteropancreatic cancer, pancreatic cancer, practice guidelines

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INTRODUCTION

Neuroendocrine tumours (NETs) are uncommon malignancies that are located throughout the body. Despite their rarity, NETs are, because of a longer survival period even in patients with incurable and metastatic disease, the second most prevalent gastrointestinal (GI) cancer after colon cancer.

Neuroendocrine tumours arise from enterochromaffin cells, with the GI tract being the most common primary site, accounting for more than 60% of NETs[1]. Gastrointestinal NETs can be divided into the clinically relevant entities of pancreatic NETs (PNETs) and gastroenterohepatic NETs. A NET is classified as functional when associated with excessive secretion of hormones, or nonfunctional when symptoms derive from the physical

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manifestations of the tumour. The incidence of NETs is increasing, likely because of better detection, improved classification, and screening programs that require more widespread use of upper- and lower-bowel endoscopy, as well as improved resolution in GI imaging techniques and a heightened awareness of the disease entity. Nevertheless, most patients in Ontario with a NET present with metastatic disease that has no option for cure and a significant effect on quality of life (QOL).

Recent data from Ontario indicated a NET incidence rate of 5.86 cases per 100,000 population, an increase of more than double during the past 15 years[1]. A recent patient experience study documents the considerable burden of disease from NETs, particularly with respect to symptoms, work and daily life, and health care resource use[2].

Neuroendocrine tumours represent an extremely heterogeneous group of malignancies with a range of clinical behaviours, making the performance of high-quality clinical studies difficult. The long natural history of low- to intermediate-grade NETs in particular makes the identification of appropriate trial endpoints challenging. However, since about 2007, sufficiently powered therapeutic trials have been successfully conducted; thus, the creation of evidence-based guidelines for management is now a timely undertaking. Guidelines produced by the rigorous evaluation of trials, particularly in a rare tumour type such as the NET, are likely to translate into improved patient care, particularly in geographically large and diverse areas such as Ontario. Furthermore, the measurement of compliance with guidelines can create a basis for practice improvement and professional development. Assimilating new evidence is particularly important to ensure equity of access to therapies for NETs that have been proved to have a significant effect on patient outcomes.

The present guideline focuses exclusively on antiproliferative therapy for GI NETs and does not address the treatment of symptoms from functional NETs. It considers the role of the major systemic therapeutic interventions for NETs: somatostatin analogues (SSAs—initially used to control the secretory symptoms of carcinoid syndrome, but subsequently shown to have an antiproliferative effect even in nonfunctional NETs); chemotherapy (which has been poorly studied in low numbers of patients, producing few high-quality data); targeted therapy (including the mammalian target of rapamycin inhibitor everolimus, and the anti–vascular endothelial growth factor agents sunitinib and bevacizumab); and various treatment combinations. The guideline does not address the role of peptide receptor radionuclide therapy. Notably, most trials did not assess QOL, which is now recognized as an essential metric in the evaluation of treatments for incurable cancer.

RESEARCH QUESTION

Which of the antineoplastic systemic therapies [chemotherapy, SSAs, interferon alfa, or targeted agents (sunitinib, everolimus, bevacizumab, pazopanib)] is most effective in improving clinical outcomes [progression-free survival (PFS), overall survival (OS), overall response rate, median survival, symptom control, biomarker decline, QOL) while minimizing adverse effects (toxicity) in patients with incurable gastroenteropancreatic NETs?

METHODS

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[3,4]. The process includes a systematic review, interpretation of the evidence, creation of draft recommendations by the members of the Working Group, internal review by content and methodology experts, and external review by clinicians and other stakeholders.

Search for Existing Systematic Reviews

A search for existing published systematic reviews sought both original reviews and reviews published as a component of practice guidelines in MEDLINE (2008 to 13 June 2016), EMBASE (2008 to 13 June 2016), the Cochrane Database of Systematic Reviews (2008 to 13 June 2016), the Canadian Agency for Drugs and Technologies in Health (27 August 2015), and the U.S. Agency for Healthcare Research and Quality (27 August 2015).

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant reviews were assessed using the AMSTAR[5] tool to determine whether they could be incorporated as part of the evidentiary base.

Search for Primary Literature

In the absence of any relevant systematic reviews, MEDLINE (2008 to 13 June 2016) and EMBASE (2008 to 13 June 2016) were searched for published phase II and III randomized controlled trials (RCTs) and non-RCTs. Reference lists of the included primary literature were scanned for additional citations. Conference proceedings (2008–2015) for the American Society of Clinical Oncology, the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, the European Society for Medical Oncology, the European Cancer Congress, the European Neuroendocrine Tumor Society, and the North American Neuroendocrine Tumor Society were also searched for relevant abstracts.

Study Selection Criteria and Process

Inclusion Criteria: Prospective (phase II and III) and retrospective studies with 20 participants or more were included if they assessed adult patients with incurable gastroenteropancreatic NETs. Of the patients evaluated for the outcomes in each study, at least 80% had to have gastroenteropancreatic NETs as opposed to NETs of other types (for example, lung, unknown primary, and so on). Studies also had to have reported on or compared the effects of any of the systematic therapies [chemotherapy, SSAs, interferon alfa, or targeted agents (sunitinib, everolimus, bevacizumab, pazopanib)] on any one or more of PFS, OS, overall response rate, or median survival, with or without biomarker decline (chromogranin A, pancreastatin, glucagon), QOL, and adverse effects.

Exclusion Criteria: Studies assessing pituitary tumours, large-cell neuroendocrine carcinoma, thymic tumours, goblet cell carcinoma, bronchial NETs, paragangliomas,

mixed NETs, pheochromocytoma, small-cell lung cancer, and thyroid cancer were excluded, as were abstracts of nonrandomized studies (single-arm clinical trials, case series, and so on), abstracts of interim analyses, papers or abstracts not available in English, letters and editorials that reported clinical trial outcomes, and papers and abstracts published before 2008.

Internal Review

Guidelines prepared by the PEBC are reviewed by a panel of content experts (the Expert Panel) and a methodology panel [the Report Approval Panel (RAP)]. Both panels must approve the document. The Working Group is responsible for incorporating the feedback from both panels.

Patient and Caregiver-Specific Consultation Group

Patients, survivors, and caregivers participated as consultation group members. They reviewed the draft recommendations and provided feedback to the Working Group's health research methodologist about comprehensibility, appropriateness, and feasibility. The health research methodologist relayed the feedback to the Working Group for consideration.

External Review

The PEBC external review process is two-pronged and includes a targeted peer review that obtains direct feedback on the draft guidelines from a small number of specified content experts, and a professional consultation that facilitates dissemination of the final guidelines to Ontario practitioners.

RESULTS

The full systematic review provides details of the methodology and clinical outcomes[6].

Literature Search Results

Existing Systematic Reviews

No relevant systematic reviews were identified. A systematic review of nonsurgical treatments for PNETs by Valle *et al.*[7] was found; however, that review was not included because of differences in inclusion criteria (that is, sample size limits and types of therapy, among others). Another systematic review of the role of targeted therapy in metastatic NETs by Lee *et al.*[8] was found. That review, published in 2016, included only RCTs and performed a meta-analysis of patients treated with targeted therapy. Although it looked at patient populations and outcomes similar to those in the present review, its results were not included for multiple reasons: heterogeneous trials were combined for a meta-analysis, results of patients with PNETs and non-PNETs were not reported separately, and different drugs in the same class were combined for analysis.

Primary Literature

The search uncovered eleven relevant randomized prospective studies[9–19], sixteen nonrandomized prospective studies[20–35], and thirteen retrospective studies[36–48]. Where multiple reports and abstracts were published for a single trial or study, only the most recent full publication was included, unless other reports contained data that were not available in the most recent publication.

Several trials included both PNETs and non-PNETs in their populations without presenting results by subgroup[9,16,19,20,23,25,35–37,39,40,43,44,46]. Because of heterogeneity and a potential for bias, those trials were not used for making the initial recommendations (PNETs and non-PNETs both respond differently to treatment, making it difficult to draw any conclusions from those trials). Although the evidence from the subgroup analyses and planned interim analyses might not be strong, the rarity of NETs, coupled with the difficulty of conducting methodologically sound trials in the affected population, requires the use of the best available evidence in making treatment decisions.

Although initially determined as outcomes of interest, biomarker decline and symptom control were not, in the end, incorporated into the present guideline because of inconsistent and incomplete reporting of those outcomes across trials.

Internal Review

Expert Panel Review

The Gastrointestinal Cancer Disease Site Group acted as the expert panel for this guideline. For approval, 75% of the Gastrointestinal Disease Site Group membership must cast a vote or abstain, and of those members who vote, 75% must approve the document. Of the 22 eligible members of the Gastrointestinal Disease Site Group, 16 members cast votes and none abstained, for a 72.7% response, June to August 2016. Of the members who cast votes, 16 approved the document (100%).

RAP Review

Three RAP members, including the PEBC director, reviewed the document in June 2016. The RAP approved the document on 4 July 2016.

Patient and Caregiver-Specific Consultation Group

Four patients, survivors, and caregivers participated as consultation group members.

External Review

Targeted Peer Review

Of 9 targeted peer reviewers from North America identified by the Working Group and considered to be clinical experts on the topic, 3 agreed to be reviewers. One response was received.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, radiation oncologists, and surgeons with an interest in GI or pancreatic or neuroendocrine or systemic gastrointestinal disease in the PEBC database (79 individuals: 75 from Ontario and 4 from out of province) were contacted by e-mail to inform them of the survey. Responses were received from 13 of the contactees (16.5%), with 7 stating that

they did not have interest in the area or were unavailable to review this guideline at the time.

RECOMMENDATIONS AND KEY EVIDENCE

PNETs

Recommendation 1

Patients with well- or moderately-differentiated PNETs should be offered targeted therapy (that is, everolimus or sunitinib). Because of insufficient evidence, no recommendation can be made for or against other types of targeted therapy, SSAs, chemotherapy, or combination therapy.

Qualifying Statements for Recommendation 1: Based on previously established trials, standards of care, and considerable years of clinical experience, chemotherapy could remain an option, although no recent RCTs have validated that approach. Methodologically strong evidence for chemotherapy, unlike that for other systemic therapy options, does not exist.

The various systemic therapy regimens, doses, and schedules have not been directly compared, meaning that the data are insufficient to recommend one approach over another. However, targeted therapy—that is, everolimus or sunitinib—is associated with the largest benefit [specifically, the lowest hazard ratio (HR) for systemic therapy].

There is no evidence to support the use of dual biologic therapy.

Subgroup analysis has shown a strong trend toward benefit with the use of SSAs in PNETs, although the HR was not statistically significant. Overinterpretation of those results is cautioned, because the subgroup analysis was not adequately powered and contained a low number of events. However, a significant benefit for SSAs was shown in the overall study population, of which PNET patients constituted approximately 45%[9].

Key Evidence for Recommendation 1: The overall quality of the evidence was assessed using the GRADE criteria. The best evidence for targeted therapy comes from two RCTs[13,17]. Based on those two trials, the overall quality of the evidence was deemed moderate, marked down for risk of bias, given that patients were able to cross over to the treatment arm at disease progression in both trials.

The overall quality of the evidence for SSAs was low because of imprecision [wide confidence interval (CI)] and risk of bias (subgroup not powered for analysis). For chemotherapy, quality was very low because of risk of bias (prospective and retrospective single-arm studies) and imprecision (low patient numbers). For combination therapy, quality was moderate because of imprecision (wide CI). The best evidence for combination therapy comes from one RCT reported in abstract form[11], which was used in assessing quality.

The RADIANT-3 trial[17], which evaluated the use of everolimus, reported a statistically significant benefit for PFS when treatment was compared with placebo (HR: 0.34; 95% CI: 0.26 to 0.44; $p < 0.001$). Median PFS duration for patients with PNETs receiving everolimus ranged from 7.6 months (95% CI: 5.52 to 7.62 months) to 14 months[10,17,21,34,45,49].

No difference in OS was observed between the arms in the RADIANT-3 trial; however, patients receiving placebo were allowed to cross over to the treatment arm after disease progression, confounding the results. A rank-preserving structural failure analysis was later performed to correct for crossover bias (HR: 3.27; 95% CI: 0.10 to 13.93)[50]. The *p* value was not reported.

A phase III randomized trial that evaluated the use of sunitinib compared with placebo[13] also reported a statistically significant benefit for PFS with treatment (HR: 0.315; 95% CI: 0.181 to 0.546; $p < 0.01$). After a 5-year follow-up, a statistically significant OS benefit was observed (HR: 0.40; 95% CI: 0.23 to 0.71; $p = 0.001$) when patients who crossed over to the treatment arm after disease progression were censored[51].

In a matching, adjusted indirect comparison of patients from the RADIANT-3 trial and the phase III sunitinib trial, no statistically significant differences in PFS ($p = 0.578$) and OS ($p = 0.383$) were observed for everolimus compared with sunitinib[52].

Preliminary findings from both the randomized phase II Cancer and Leukemia Group B 80701[10] and COOPERATE-2 trials[11], which are available only in abstract form, showed no statistically significant differences in PFS between patients receiving everolimus plus bevacizumab and those receiving everolimus alone (HR: 0.80; 95% CI: 0.55 to 1.17; $p = 0.12$) or between patients receiving everolimus plus pasireotide and those receiving everolimus alone (HR: 0.99; 95% CI: 0.64 to 1.54).

A subgroup analysis of patients with PNETs in the CLARINET trial[53] reported no benefit for lanreotide with respect to PFS (HR: 0.58; 95% CI: 0.32 to 1.04). The *p* value was not reported. However, the overall study[9] showed a significant PFS benefit with treatment (HR: 0.47; 95% CI: 0.30 to 0.73; $p < 0.001$) in a population that included approximately 45% patients with PNET.

Non-PNETs

Recommendation 2

Patients with non-PNETs should be offered either targeted therapy (that is, everolimus) or either of the SSAs octreotide long-acting repeatable (LAR) or lanreotide. Because of insufficient evidence, no recommendation can be made for or against other types of targeted therapy, other SSAs, chemotherapy, or combination therapy.

Qualifying Statements for Recommendation 2: The evidence for everolimus is specific to patients with non-functional tumours and is based on a subgroup analysis of patients with GI NETs, although the results of a preceding trial suggested some benefit for patients with functional tumours receiving everolimus with octreotide LAR. However, uncertainty accompanies those results, because that trial did not meet its pre-specified endpoint for analysis and contained a small percentage of patients with PNETs and lung NETs.

The various targeted therapy and SSA regimens, doses, and schedules have not been directly compared, meaning that the data are insufficient to recommend one over another or any preferred method of sequencing.

Key Evidence for Recommendation 2: The quality of the evidence was assessed using the GRADE criteria.

The best evidence for targeted therapy comes from one RCT[15], which was used to determine the overall quality of the evidence. That RCT was considered to be of moderate quality, being marked down for risk of bias (subgroup not powered for analysis).

The best evidence for SSAs comes from two RCTs[9,14], which were used to determine the overall quality of the evidence. Those RCTs were considered to be of low quality, being marked down for imprecision (low patient numbers) and risk of bias (subgroup not powered for analysis). Although the quality of the evidence might be low, the magnitude of the benefit in the trials is large.

The RADIANT-4 trial demonstrated benefit for everolimus in the GI subgroup of patients with nonfunctional NETs, with a median PFS duration in the treatment and control arms of 13.1 months (95% CI: 9.2 to 17.3 months) and 5.4 months (95% CI: 3.6 to 9.3 months) respectively (HR: 0.56; 95% CI: 0.37 to 0.84)[15]. The *p* value was not reported.

Two studies reported on octreotide. In a planned interim analysis for the PROMID study by Rinke *et al.*[14], a significant benefit in tumour progression or tumour-related death, considered to be a surrogate for PFS, was demonstrated for the treatment arm over the control arm (HR: 0.34; 95% CI: 0.20 to 0.59; $p = 0.000072$). However, no difference in survival was found (HR: 0.83; 95% CI: 0.47 to 1.46; $p = 0.51$)[54]. Meanwhile, a retrospective study reported a median PFS duration of 51.0 weeks (95% CI: 26.4 to 75.6 weeks) with the use of octreotide[42].

The RADIANT-2 trial suggested some PFS benefit for patients with functional tumours receiving everolimus plus octreotide LAR (HR: 0.77; 95% CI: 0.59 to 1.00; $p = 0.026$)[19] even though the CI reaches 1. Furthermore, the trial did not meet its pre-specified endpoint for analysis and contained a small percentage of patients with PNETs and lung NETs.

In the CLARINET trial[9,55], a subgroup analysis of patients with midgut NETs reported a PFS benefit with lanreotide (HR: 0.35; 95% CI: 0.16 to 0.80; $p = 0.009$). A subgroup analysis of patients with hindgut NETs did not show a benefit with lanreotide, which could be a result of the very low number of patients in the subgroup ($n = 14$).

The literature search identified no studies that specifically assessed or reported on the role of chemotherapy in patients with non-PNETs.

CONCLUSIONS

Patients with well- or moderately-differentiated PNETs should receive targeted therapy (that is, everolimus or sunitinib), and patients with non-PNETs should be offered either targeted therapy (that is, everolimus) or one of the SSAs octreotide LAR or lanreotide. Evidence from two phase III trials demonstrated a significant PFS benefit for patients with PNETs. For patients with non-PNETs, the evidence comes from subgroup analyses of RCTs and a planned interim analysis. Although the evidence has its limitations, the rarity of NETs, coupled with the difficulty of conducting methodologically sound trials in the affected population, requires the use of the best available evidence to make treatment decisions.

Because of insufficient evidence for both PNETs and non-PNETs, no evidence-based recommendation can be made for or against other types of targeted therapy, other SSAs, chemotherapy, or combination therapy. A number of studies have evaluated various therapies and combinations; however, many were not randomized or comparative and contain small numbers of patients. As a result, a need for randomized studies that compare systemic therapies remains.

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CONFLICT OF INTEREST DISCLOSURES

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent from the Ontario MOHLTC.

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SS has received research funding from Novartis and was a local principal investigator for the RADIANT-4 trial. TA has received fees as a consultant to Novartis and Ipsen, has received grants and research support from Novartis, and has published an editorial on the topic addressed by this guideline. CL has received travel grants and grants and research support from Novartis, has published consensus guidelines and other publications on the topic addressed by this guideline, and is Chief of the Odette Cancer Centre, which receives support from Novartis and Ipsen. DS, CC, NH, RW, and KZ have no conflicts of interest to declare.

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