Guideline 2-21 REQUIRES UPDATING

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

Systemic Therapy of Incurable Gastroenteropancreatic Neuroendocrine Tumours

S. Singh, D. Sivajohanathan, T. Asmis, C. Cho, N. Hammad, C. Law, R. Wong, K. Zbuk and the Gastrointestinal Disease Site Group

Report Date: December 9, 2016

An assessment conducted in February 2020 indicated that Guideline 2-21 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 2-21 is comprised of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31861

| Section 1: | Recommendations |
| Section 2: | Guideline - Recommendations and Key Evidence |
| Section 3: | Guideline Methods Overview |
| Section 4: | Systematic Review |
| Section 5: | Internal and External Review |

For information about this document, please contact Dr. Simron Singh, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca
Guideline 2-21

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


Copyright
This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer
Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.
Systemic Therapy of Incurable Gastroenteropancreatic Neuroendocrine Tumours

Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES
To make recommendations with respect to systemic therapy for the treatment of patients with incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs).

TARGET POPULATION
Adults with a diagnosis of incurable GEP NETs.

INTENDED USERS
Clinicians involved in the treatment of patients with GEP NETs.

Note: This guideline does not address peptide receptor radionuclide therapy. This is covered in Guideline 12-13. Further, this guideline addresses anti-proliferative treatment and not symptomatic treatment.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

<table>
<thead>
<tr>
<th>Recommendation 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with well or moderately differentiated pancreatic neuroendocrine tumours (pNETs) should be offered targeted therapy (i.e., everolimus or sunitinib). No evidence-based recommendation can be made for or against other types of targeted therapy, somatostatin analogues, chemotherapy or combination therapy due to insufficient evidence.</td>
</tr>
</tbody>
</table>

Qualifying Statements for Recommendation 1

- Based on previously established trials, standard of care, and considerable years of clinical experience, chemotherapy may remain an option although there have been no recent randomized controlled trials conducted to validate this. Methodologically strong evidence for chemotherapy does not exist, unlike other systemic therapy options.
- The various systemic therapy regimens, doses, and schedules have not been directly compared with one another, resulting in insufficient data to recommend one over the other. However, targeted therapy (i.e., everolimus or sunitinib) is associated with the largest benefit (i.e., lowest hazard ratio [HR]) for systemic therapy.
- There is no evidence to support the use of dual biological therapy.
- Subgroup analysis has shown a strong trend toward benefit in the use of somatostatin analogues in pNETs although the HR was not statistically significant. Over-interpretation of these results is cautioned as the subgroup analysis was not adequately powered and contained a low number of events. However, the overall study population did show a significant benefit for SSAs and was comprised of approximately 45% pNET patients [1].
**Recommendation 2**

- Patients with non-pNETs should be offered either targeted therapy (i.e., everolimus) or somatostatin analogues (i.e., octreotide long-acting repeatable [LAR] or lanreotide). No evidence-based recommendation can be made for or against other types of targeted therapy, somatostatin analogs, chemotherapy, or combination therapy due to insufficient evidence.

**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 gastrointestinal patients, although the results of a preceding trial suggest some benefit for patients with functional tumours receiving everolimus with octreotide LAR. However, there is uncertainty surrounding these results as this trial did not meet its pre-specified endpoint for analysis and contained a small percentage of patients with pancreatic and lung NETs.

- The various targeted therapy and somatostatin analogue regimens, doses, and schedules have not been directly compared with one another, resulting in insufficient data to recommend one over the other or any preferred method of sequencing.