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The Role of Octreotide in the Management of Patients with Cancer

Practice Guideline Report #12-7

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ORIGINAL GUIDELINE: May 2003
NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: August 2004
MOST RECENT LITERATURE SEARCH: July 2004

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Questions

1. Does treatment with octreotide have advantages over standard measures in controlling diarrhea induced in cancer patients by particular chemotherapy regimens?
2. Can therapy with octreotide reduce complications and mortality after surgery for pancreatic cancer?
3. For patients with carcinoid and other neuroendocrine tumours secreting vaso-active substances, can treatment with octreotide relieve debilitating symptoms and improve quality of life and/or survival?
4. In terminally ill cancer patients, does treatment with octreotide help to relieve chronic bowel obstruction, avoid the use of nasogastric tubes, and improve quality of life?
5. In advanced malignancies, does treatment with octreotide as an anti-tumour agent improve outcomes such as tumour response, quality of life, and survival?

Methods

The literature was searched using the MEDLINE (Ovid) (1966 through October 2002), CANCERLIT (Ovid) (1983 through October 2002), and Cochrane Library (Issue 4, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials.

Evidence was selected and reviewed by a medical oncologist, a surgeon, two members of the Practice Guidelines Initiative's Systemic Treatment Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Systemic Treatment Disease Site Group, which comprises medical oncologists, pharmacists, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report will be obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline information.

Update

The original literature search has been updated using MEDLINE (October 2002 through July 2004), EMBASE (September 2002 through July 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2004), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to July 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal Practice Guidelines Initiative project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

1. OCTREOTIDE IN THE TREATMENT OF CHEMOTHERAPY-INDUCED DIARRHEA

Question

Does treatment with octreotide have advantages over standard measures in controlling diarrhea induced in cancer patients by particular chemotherapy regimens?

Target Population

These recommendations apply to adult cancer patients receiving chemotherapy, including 5-fluorouracil (5-FU) and/or cisplatin, who have developed diarrhea sufficiently profuse to put them at risk for dehydration (generally National Cancer Institute Common Toxicity Criteria grade 3/4).

Recommendation

- For chemotherapy-induced diarrhea, octreotide is recommended at a dose of 100 µg subcutaneously three times daily and escalating every eight hours by 50 to 100 µg until the diarrhea is controlled, to a maximum of 500 µg three times daily.

Qualifying Statement

- For patient convenience, an alternative, albeit less effective, option is standard oral anti-diarrheal agents in the usual approved doses (e.g. loperamide 4 mg initially, then 2 mg after every unformed stool, up to a maximum of 16 mg/day). If the diarrhea has not substantially improved in 24 hours, or if the patient requires intravenous rehydration, then octreotide should be initiated.

Key Evidence

- In four small randomized trials, octreotide controlled diarrhea induced by chemotherapy with 5-FU and/or cisplatin significantly better than loperamide.
- When data on complete resolution of chemotherapy-induced diarrhea from three randomized trials were pooled, there was an observed benefit for octreotide when compared with loperamide (overall risk ratio, 0.16; 95% confidence interval, 0.08 to 0.34; $p<0.0001$).

Future Research

- The mechanism of diarrhea in patients receiving chemotherapy with CPT-11 (irinotecan) would also suggest that octreotide might be an effective anti-diarrheal agent. Octreotide should be examined where standard anti-diarrheal agents have proved incapable of stopping diarrhea induced by chemotherapy with CPT-11 and patients have required intravenous hydration.
- Further research is required to identify clinical situations where severe diarrhea is anticipated that would allow the initiation of octreotide as first-line treatment.

2. OCTREOTIDE FOLLOWING PANCREATIC SURGERY

Question

Can therapy with octreotide reduce complications and mortality after surgery for pancreatic cancer?

Target Population

These recommendations apply to patients undergoing pancreatic surgery for pancreatic cancer.

Recommendations

- Octreotide, administered at a dose of 100 µg subcutaneously three times daily starting one hour prior to surgery and continuing for seven days is recommended as part of the standard management for patients undergoing pancreatic surgery.

Key Evidence

- In three large, placebo-controlled double-blind randomized trials, there were significant decreases in serious complications (pancreatic fistula, abscess, and fluid collection) in the patients receiving octreotide. There were no differences between octreotide and placebo in mortality following surgery in any of the trials.

Update

- Three randomized trials identified in an update of the literature did not detect any significant differences in serious complications or mortality with the addition of octreotide to surgical resection.

3. OCTREOTIDE FOR SYMPTOM RELIEF OF CARCINOID AND OTHER NEUROENDOCRINE TUMOURS

Question

For patients with carcinoid and other neuroendocrine tumours secreting vaso-active substances, can treatment with octreotide relieve debilitating symptoms and improve quality of life and/or survival?

Target Population

These recommendations apply to patients with carcinoid and other neuroendocrine tumours who have had no improvement in symptoms following chemotherapy or those who present with debilitating neuroendocrine symptoms (i.e. profuse diarrhea).

Recommendations

- Octreotide is recommended to control symptoms associated with carcinoid tumours.
- Because the mechanism of action and the pathophysiology of other secretory neuroendocrine tumours are similar to that of carcinoid tumours, it is reasonable to recommend octreotide to control symptoms associated with secretory neuroendocrine tumours.
- It is suggested that octreotide be administered in a subcutaneous dose of 100 µg three times daily, or 200 µg twice daily, with an increase in the dose of 50 to 100 µg every eight or twelve hours until symptom control is achieved.

Key Evidence

- In three small randomized trials, octreotide significantly reduced episodes of flushing and diarrhea in patients with secretory carcinoid tumours. Short-acting octreotide was compared with placebo in three trials, different doses of a long-acting formulation in the fourth, and to lanreotide (a long-acting somatostatin inhibitor) in the fifth.
- Small studies in other neuroendocrine tumours suggest that symptoms associated with hormonal secretion can be improved with octreotide administration.

Future Research

- Further studies should be performed to confirm the efficacy of a long-acting formulation of octreotide in patients with secretory neuroendocrine tumours.

4. OCTREOTIDE IN PATIENTS WITH CHRONIC BOWEL OBSTRUCTION

Question

In terminally ill cancer patients, does treatment with octreotide help to relieve chronic bowel obstruction, avoid the use of nasogastric tubes, and improve quality of life?

Target Population

These recommendations apply to terminally ill cancer patients with inoperable bowel obstruction.

Recommendations

- In patients with inoperable bowel obstruction due to advanced cancer, the use of octreotide 300 µg daily by subcutaneous infusion may be considered for the purpose of reducing symptoms such as nausea, vomiting, and pain, as well as the need for a nasogastric tube.

Key Evidence

- Two small randomized trials, one comparing octreotide to hyoscine butylbromide and the other to scopolamine butylbromide, were reviewed. Three single-arm studies were also reviewed. The data from the randomized trials demonstrated superior symptomatic relief for octreotide compared with butylbromide in terms of nausea, vomiting, pain, and nasogastric secretions.

Update

- One trial detected significant differences in favour of octreotide over hyoscine butylbromide for episodes of vomiting and nausea from time 1 to time 2, and in fatigue and anorexia in relation to symptom improvement. No significant differences in pain were reported between the two treatment groups.

Future Research

- Further larger randomized studies should be performed to evaluate quality of life as well as symptomatic endpoints.

5. OCTREOTIDE AS AN ANTI-TUMOUR AGENT IN ADVANCED MALIGNANCIES

Question

In advanced malignancies, does treatment with octreotide as an anti-tumour agent improve outcomes such as tumour response, quality of life, and survival?

Target Population

These recommendations apply to patients with metastatic breast cancer, advanced colorectal, stomach, or pancreatic cancer, or unresectable malignant hepatoma.

Recommendations

- Octreotide cannot be recommended as an anti-tumour agent for the treatment of metastatic breast cancer, advanced pancreatic, or asymptomatic colon cancer.
- Further studies in advanced breast, colon, or pancreatic cancer are unlikely to be productive unless a different formulation or dose schedule is anticipated to be more active.

Key Evidence

- Early encouraging results of small randomized trials in patients with metastatic breast and gastrointestinal cancer have not been confirmed by larger, tumour-specific trials in breast, colon, and pancreatic cancer.
- A small randomized trial in patients with malignant hepatoma demonstrated improved survival and symptom control in patients receiving octreotide. These results should be regarded as preliminary and further randomized trials are needed.

Update

- For patients with advanced hepatocellular carcinoma, one small randomized trial did not detect any significant survival benefit with octreotide when compared with control.

Future Research

- Preliminary data in advanced hepatoma are interesting but need to be confirmed in a large randomized study of octreotide versus placebo.
- The use of octreotide as an adjuvant treatment, in combination with tamoxifen in early-stage breast cancer, is still under evaluation. The increased incidence of significant gallbladder toxicity in one randomized trial of octreotide in early operable breast cancer suggests that this would not be an advisable approach.
- The dosage and scheduling of regular and long-acting octreotide should be investigated further.
- If octreotide is to be investigated in other metastatic or earlier-stage cancers, attention should be paid to the design of such trials: e.g. use of placebo controls, separate studies in different disease entities.

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This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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