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Practice Guideline Report 12-7 EDUCATION AND INFORMATION 2012

The Role of Octreotide in the Management of Patients with Cancer

Members of the Systemic Treatment Guideline Development Group

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

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This Evidence-based Series (EBS) report consists of 3 sections:
Section 1: Summary (ARCHIVED)
Section 2: Systematic Review
Section 3: Document Review Summary
and is available on the CCO Web site (http://www.cancercare.on.ca)
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version May 2003	1966 to 2002	Full Report	Peer review publication Web publication	Not Applicable
Update Aug 2004	2002-2004	New data added to original Full Report	Updated Web publication	NA
Reviewed version June 2013	2000 to 2011	New data found in Document Assessment and Review Tool	Updated Web publication	2003 guideline is ARCHIVED

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The Role of Octreotide in the Management of Patients with Cancer
Practice Guideline Report #12-7

P. Major, A. Figueredo, V. Tandan, V. Bramwell, M. Charette, T. Oliver, and members of the Systemic Treatment Disease Site Group

ORIGINAL GUIDELINE: May 2003
NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: August 2004
MOST RECENT LITERATURE SEARCH: 2012

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.

For further information about this practice guideline, please contact: Dr. Brent Zanke, Chair, Systemic Treatment Disease Site Group, Cancer Care Ontario, 620 University Avenue Toronto, Ontario, Canada M5G 2L7 Tel: 416-9800 x2229 Fax: 416-217-1281

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/access_PEBC.htm for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

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.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
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Disclaimer

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FULL REPORT

I. 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?

II. CHOICE OF TOPIC AND RATIONALE

Somatostatin is a cyclic peptide consisting of 14 amino acids which exerts an inhibitory regulatory role in the central nervous system, hypothalamus and anterior pituitary gland, the gastrointestinal tract, the exocrine and endocrine pancreas, and the immune system (1). Somatostatin has also been observed to interfere with growth factors and possibly have a direct antiproliferative effect on some tissues (2). It has a short half-life (less than three minutes) (1), which is a drawback for therapeutic use and so somatostatin analogues have been synthesized. Octreotide is the synthetic octapeptide analogue of somatostatin.

Ampoules of octreotide have been available on the Canadian market since August 1989. A multidose vial was added in December 1995, and a long-acting suspension became available in January 1999. The ampoules and multidose injections are usually given by subcutaneous injection but can be given by the intravenous route. The long-acting suspension is intended for deep intragluteal injection only.

Octreotide has approval from the Therapeutic Products Directorate for the control of symptoms in patients with carcinoid tumours and vasoactive intestinal peptide (VIP) tumours, acromegaly, prevention of complications following pancreatic surgery, and bleeding gastro-esophageal varices. The long-acting suspension is indicated for acromegalic patients and patients with carcinoid tumours or VIP-secreting tumours who are adequately controlled with octreotide administered subcutaneously. It has also been used in practice in patients with diarrhea resulting from treatment with chemotherapy, in patients with advanced breast and gastrointestinal cancers, and in terminally ill cancer patients suffering from bowel obstruction. It is a drug that is used for many indications and controversy exists over its efficacy for certain of these indications.

With the potential for variability in practice in Ontario, the Systemic Treatment Disease Site Group (DSG) felt it would be useful to perform a systematic review of the best available evidence on this topic.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care using methods of the Practice Guidelines Development Cycle (3). Evidence was selected and reviewed by a medical oncologist, a surgeon, two members of the PGI's Systemic Treatment DSG, and methodologists. Members of the Systemic Treatment DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of octreotide in cancer patients, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to enable evidence-based practice. The Practice Guidelines Initiative is

editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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 (PGCC).

The PGI 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.

Literature Search Strategy

The literature was searched using the MEDLINE (Ovid) (1966 through November 2002), CANCERLIT (Ovid) (1983 through November 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.

The literature search combined disease specific terms (neoplasms/ or cancer:.mp. or carcinoma:mp. or malignan:.mp. or tumo?r:.mp.) with treatment specific terms (octreotide/ or octreotide.mp. or somatostatin.mp. or sandostatin.mp. or SMS-201-995.mp.) and search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and clinical trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Randomized trials comparing octreotide with placebo, observation, or other treatment in cancer patients for the indications mentioned in the guideline questions.
- Non-controlled reports of octreotide were considered only for questions three (neuroendocrine tumours) and four (chronic bowel obstruction).
- Outcomes of interest, including tumour response, survival, symptom relief or control, and quality of life were reported.

Exclusion Criteria

- Letters and editorials were not considered.
- Papers published in a language other than English were not considered.

Synthesizing the Evidence

The results of three randomized trials comparing octreotide to loperamide for the resolution of chemotherapy-induced diarrhea were pooled, using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). Pooled results were expressed as a relative risk (RR) with a 95% confidence interval (CI) and percent relative risk reduction (RRR). Relative risk reduction compares the risk of target events in the treatment group with the risk of target events in the control group (RRR=1-RRx100); Relative risk ratio measures the proportion of patients in the experimental group, relative to the proportion of patients in the control group, who are likely to experience the event. When the event measured is unfavourable (e.g. diarrhea), estimates greater than 1.0 favour the control group (eg. loperamide therapy), and estimates less than 1.0 favour the experimental group (eg. octreotide therapy). The fixed effects model was used in the meta-analyses because there were too few studies to estimate random effects. A statistical Q-test was used to measure statistical heterogeneity.

It was judged inappropriate to pool the results of any other section because of extensive heterogeneity in trial design and reporting of outcomes of interest.

IV. RESULTS

Literature Search Results

A classification of the literature is found in Table 1. Where the results of a trial have been reported or updated in more than one publication, only the most recent publication is included.

Table 1. Literature included in this practice guideline report.

Indication	Number of Reports		Reference Numbers	Summary of Results
	Full Reports	Abstracts		
1. Treatment of chemotherapy-induced diarrhea				
Practice Guidelines	2	0	4,5	
Randomized Trials	6	0	6-11	Table 2
Update				
Randomized trial	0	1	1u	
2. Octreotide following pancreatic surgery				
Randomized Trials	3	0	12-14	Table 3
Update				
Randomized trials	3	0	2u-4u	
3. Symptom relief of neuroendocrine tumours				
Practice Guideline	1	0	5	Section 3
Randomized Trials	5	0	15-19	Table 4
Systematic Review of Dose Titration	1	0	20	
Non-randomized trials	15	0	21-35	
4. Octreotide use in chronic bowel obstruction				
Randomized Trials	2	0	36, 37	Table 5
Non-randomized Trials	3	0	38-40	
Update				
Randomized Trials	1	0	5u	
5. Anti-tumour effects in advanced malignancies				
Randomized Trials	7	2	41-49	Table 6
Update				
Randomized Trials	1	0	6u	

1. 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?

The severity of diarrhea can be graded by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (see Appendix 1) with grade 3 and 4 predicting the greatest risk of death, but Wadler et al (4) suggested that there are certain deficiencies with this grading system. They recommend the incorporation of a number of other factors such as number of days the patient has experienced diarrhea, stool volume, number of stools per day, skin integrity, and bacteremia from intestinal flora.

Results

Literature Search Results

Six randomized trials, including a total of 235 randomized patients, have investigated the efficacy of octreotide for the management of diarrhea induced by certain chemotherapy regimens (6-11). The results of the trials are summarized in Table 2. In addition, two practice guidelines (4,5) were located that give recommendations for octreotide use for the control of chemotherapy-induced diarrhea.

With the exception of one trial (8), none of the reviewed studies were blinded or placebo-controlled. The chemotherapy regimens consisted of 5-FU in four of the trials (6,9-11), cisplatin in one trial (8), and the final study (7) did not mention the chemotherapy regimen except to indicate that it was intensive. Octreotide was compared with placebo (8) or loperamide (7,9-11). One study compared two different doses of octreotide (6).

Octreotide was administered subcutaneously in all but one trial (7), where it was administered intravenously over 24 hours. The dose of octreotide varied from study to study, as did the dose of loperamide in the studies where it was used.

The severity of the chemotherapy-induced diarrhea varied across studies. Three studies included only patients with greater than seven stools per day (6,9,11). Cascinu et al (8,10) included patients with three to nine stools per day and excluded patients with stool frequency exceeding nine per day. Gellar et al (7) included patients with a daily stool volume of 600 ml or greater.

Update

A randomized trial of two doses of long-acting octreotide reported as an abstract was identified in the update of the literature (1u). As an interim analysis, limited data are available on 118 patients randomized to 30 mg or 40 mg of long-acting octreotide for the treatment of chemotherapy-induced diarrhea.

Table 2. Results of studies examining chemotherapy-induced diarrhea.

Author Year (Ref.)	No. rand. pts.	Population	Chemo-therapy	Inter-ventions	Drug Dosage	% Pts. with complete resolution
Goumas 1998 (6)	59	colorectal H&N	5-FU	octreotide octreotide	100 µg sc tid 500 µg sc tid	61% 90% p<0.05
Geller 1995 (7)	36	BMT leukemia	intensive	octreotide loperamide	150 µg IV over 24 hrs. 4 mg qid, orally	45%* 86%* p=0.033
Cascinu 1994 (8)	43	soft tissue sarcoma, ovary, lung, H&N	cisplatin	octreotide placebo	100 µg sc bid 100 µg sc bid	95% 25% p=0.01
Nikou 1994 (9)	16	colorectal, gastric, leukemia	5-FU	octreotide loperamide	100 µg sc tid 2 mg qid, orally	100% 0% p=NR
Cascinu 1993 (10)	41	colon, stomach, pancreas, breast	5-FU	octreotide loperamide	100 µg sc tid for 3 days 2 mg qid, 3 days orally	90% 15% p<0.005
Gebbia 1993 (11)	40	breast, gastric, colorectal, H&N	5-FU	octreotide loperamide	500 µg sc tid 4 mg tid orally	80% 30% p<0.001
Update						
Rosenoff 2004 (1u)	NR NR	colorectal other	various	octreotide octreotide	30 mg q28 days† 40 mg q28 days†	64%‡ 57%‡ p=NR

Note: 5-FU = 5-fluorouracil; bid = twice daily; BMT = bone marrow transplant; H&N = head and neck; IV = intravenously; No., = number of; NR = not reported; pts. = patients; qid = four times daily; rand. = randomized; sc = subcutaneous injection; tid = three times daily

* major response at 48 hours defined as ≥50% decrease from baseline stool volume over last 24 hours

† octreotide administered 7-14 days apart for the first two doses and every 28 days thereafter.

‡ patients with no grade III/IV diarrhea at dose 3.

Outcomes

Complete resolution of diarrhea was the major endpoint in five of the studies (6,8-11). Major response was an endpoint in the sixth study (7), with a major response defined as a 50% or greater decrease in stool volume. Significant differences in favour of octreotide were reported in three trials (8,10,11) (Table 2). None of the patients randomized to loperamide in the study by Nikou et al (9) experienced complete resolution of diarrhea, compared with 100% of the patients randomized to octreotide (p value not reported). Gellar et al (7) also detected a significant difference between study groups, but the difference was in favour of loperamide. In the study by Goumas et al (6), the 500 µg dose of octreotide three times daily resolved diarrhea in a significantly greater proportion of patients (90% vs. 61%; p<0.05) than the 100 µg dose three times daily.

In addition to the RCTs, two practice guidelines were located that give clinical recommendations for octreotide use in chemotherapy-induced diarrhea. Following a review of the literature, Harris et al (5) recommended initial treatment of diarrhea induced by standard-dose regimens of chemotherapy with

100 µg of octreotide subcutaneously three times daily followed by upward titration until symptoms are controlled. In situations where chemotherapy is administered at high doses, they state that octreotide may be given at a rate of 300 µg/day intravenously for 48 hours. Wadler et al (4) recommended the administration of loperamide for initial therapy for low-grade diarrhea. In this paper, the panel indicated that octreotide therapy should be considered for patients who have severe diarrhea or diarrhea that is refractory to loperamide. The panel did not give dose recommendations, as they stated that there is no clear understanding of the optimal dosage of octreotide.

Update

No significant differences in diarrhea control were reported in patients randomized to receive either 30 mg or 40 mg of long-acting octreotide (1u). While mature results are not yet available, the overall incidence of grade III/IV diarrhea at dose two was 38% and 33% and dose three was 36% and 43% for octreotide 30 mg and 40 mg respectively.

Adverse Effects

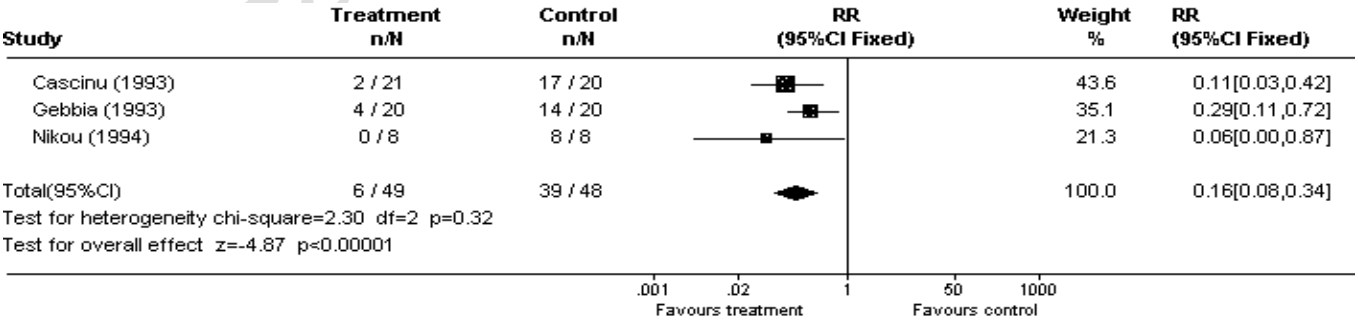
Adverse effects attributed to octreotide treatment were reported in two trials. Gebbia et al (11) reported that 15% of patients receiving octreotide had pain at the injection site, and 15% of patients receiving octreotide experienced mild abdominal pain. Gellar et al (7) reported two patients with mild elevations in total bilirubin, which resolved following completion of octreotide treatment. Another patient in this trial experienced abdominal cramping.

Pooling Results across Trials

The results of three RCTs (9-11) examining octreotide versus loperamide in patients receiving 5-FU were combined in a pooled analysis to calculate combined estimates of treatment efficacy or harm (Figure 1). A fourth trial comparing octreotide to loperamide (7) was not included in the analysis because the trial did not report on the percentage of patients experiencing complete resolution of diarrhea. The studies by Cascinu et al (8) and Goumas et al (6) reported on the percentage of patients with complete resolution of diarrhea; however the treatment arms were judged to be too different to be included in the meta-analysis.

Figure 1 shows the results of the meta-analysis for the three trials involving 97 patients with diarrhea following chemotherapy with 5-FU. The proportions of patients not experiencing complete resolution of chemotherapy-induced diarrhea were combined to obtain a more precise estimate of the treatment effect of octreotide. A statistical Q-test showed no significant statistical heterogeneity across studies for the outcome of interest. When data from the three trials were combined, there was an observed benefit for octreotide. The overall RR is 0.16 (95% CI, 0.08 to 0.34; p<0.0001). This translates into a RRR of 0.84, or 84%.

Figure 1. Meta-analysis of octreotide versus loperamide for the treatment of chemotherapy-induced diarrhea.



Interpretive Summary

Six randomized trials examining octreotide use in patients with chemotherapy-induced diarrhea were reviewed. In all but one (9), the use of octreotide was associated with a significant improvement in diarrhea. The results of the meta-analysis, considering only the three trials using complete resolution

of diarrhea as a main outcome, also detected a significant effect with octreotide. The evidence is the strongest for 5-FU chemotherapy, as this is where it has been studied most extensively.

Two of the trials comparing octreotide and loperamide for the control of chemotherapy-induced diarrhea used modest doses of loperamide (9,10) (Table 3). However, higher doses of loperamide were used in two trials (7,9), suggesting that octreotide is superior to loperamide even when the latter is used in higher doses.

No trials have evaluated the efficacy of octreotide in cases resistant to standard anti-diarrheal agents.

Based on the available evidence, octreotide is more efficacious than loperamide. However, for patients who prefer the convenience of standard oral anti-diarrheal agents over subcutaneous or intravenous octreotide, it would seem reasonable to initially try loperamide in the usual approved dose. If loperamide does not lead to improvement of diarrhea in 24 hours, or if the patient requires intravenous hydration, then octreotide should be initiated.

The trial by Goumas et al (6) demonstrated a dose-response effect of octreotide. Significantly better control of diarrhea was achieved at a dose of 500 µg three times daily. However, other trials have demonstrated significant effects at doses of 100 µg three times daily (8,10). For this reason, it is recommended that treatment should be initiated at a dose of 100 µg subcutaneously three times daily, as a patient may experience effective control of diarrhea at this dose. Escalation should proceed at increments of 100 µg three times daily to a maximum dose of 500 µg three times daily until control of diarrhea is achieved.

The majority of the trials reviewed for this section involved patients with diarrhea following chemotherapy with 5-FU. However, 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 prove incapable of stopping diarrhea induced by chemotherapy with CPT-11, and patients have required intravenous hydration.

Update

Preliminary data from a randomized trial of two doses of long-acting octreotide do not influence the interpretation of the data, or affect the recommendations.

2. Octreotide following pancreatic surgery

Question

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

Pancreatic surgery is associated with complications related to exocrine pancreatic secretion including peri-pancreatic fluid collection, fistulas, abscesses or abscess formation. Octreotide has been shown to decrease gastrointestinal secretions, and the theory behind its use in pancreatic surgery is that, if pancreatic fluid secretions are decreased, the risk of complications is minimized.

Results

Literature Search Results

Three large, multicentre, placebo-controlled, double-blind randomized trials involving a total of 843 patients were located that evaluated the use of octreotide following pancreatic surgery for cancer or inflammatory disease (Table 3) (12-14). In all three trials, patients randomized to octreotide received subcutaneous injections of 100 µg three times daily, beginning one hour prior to surgery and continuing for seven days. These studies all measured the rate of complications (pancreatic fistula, abscess, and fluid collection), and mortality. Pancreatic fistula was defined in the three trials as drain output fluid with a high amylase concentration (more than three times the maximum normal value), exceeding 10 ml/day for at least four days, from postoperative day four. Abscess was defined as the collection of pus or infected fluid confirmed either by ultrasound or computed tomograph-guided aspiration and culture or by a second laparotomy. Fluid collection was diagnosed by ultrasound or computed tomography scans and was not identifiable as an abscess.

Update

Three trials were identified in the update of the literature were identified and included in Table 3 below.

Table 3. Randomized trials of octreotide in pancreatic surgery.

Author Year (Ref) Country	Treatment Groups	Number of patients		Complication Rate		Pancreatic Fistula		Mortality	
		Overall	Pancreatic tumours	Overall	Pancreatic tumours	Overall	Pancreatic tumours	Overall	Pancreatic tumours
Montorsi 1995 (12) Italy	octreotide 100 µg tid placebo	111 107	72 67	22% 36% p<0.05	NR NR	9% 20% p<0.05	NR NR	8% 6% p=NS	NR NR
Bassi 1994 (13) Italy	octreotide 100 µg tid placebo	122 130	76 86	16% 29% p=0.01	22% 35% p=NS	9% 19% p=0.03	22% 35% p=NS	2% 4% p=NS	NR NR
Friess 1994 (14) Germany	octreotide 100 µg tid placebo	125 121	68 71	32% 55% p<0.01	38% 65% p<0.01	NR NR	24% 41% p=NR	3% 6% p=NS	3% 10% p=NR
Update									
Suc 2004 (2u) France	octreotide 100 µg tid control	122 108	104 96	22% 32% p=NS	23% 33% p=NS	17% 19% p=NS	NR NR	12% 7% p=NS	NR NR
Yeo 2000 (3u) USA	octreotide 250 µg tid control	104 107	60 63	40% 34% p=NS	NR NR	11% 9% p=NS	NR NR	1% 0% p=NS	NR NR
Lowy 1997 (4u) USA	octreotide 150 µg tid control	57 53	45 39	30% 25% p=NS	NR NR	12% 6% p=NS	NR NR	2% 0% P=NS	NR NR

Note: eval. = evaluable; No. pts. = number of patients; NR = not reported; NS = not significant; PC = pancreatic cancer; tid = three times daily.

Outcomes

Montorsi et al (12) randomized 278 patients eligible for an elective pancreatic resection for neoplastic or chronic inflammatory disease of the pancreas. Sixty patients were eliminated from the study because of protocol violation (six patients) or unresectability (54 patients). One hundred and eleven evaluable patients were randomized to receive octreotide, and 107 to receive placebo. The overall complication rate was significantly lower with octreotide (22% [octreotide] vs. 36% [placebo]; p<0.05). It was not possible to separate mortality or complication rate for patients with pancreatic cancer from patients with other pancreatic disorders.

Bassi et al (13) randomized 303 patients to octreotide or placebo prior to elective pancreatic surgery for tumours of the pancreas or for chronic pancreatitis. Twenty cases were excluded from the analysis because they were found to need surgical procedures other than those indicated in the study protocol. An additional 31 patients were found to have unresectable lesions and were also excluded from the analysis, leaving 252 evaluable patients. The overall rate of complications was significantly higher in patients receiving placebo versus octreotide (29% vs. 16%; p=0.01). Of the 252 evaluable patients, 162 had been diagnosed with pancreatic cancer and were considered high risk. Although patients with pancreatic cancer receiving placebo had a greater complication rate than octreotide, the difference for this subgroup did not reach statistical significance. When each complication was compared individually, only the incidence of pancreatic fistulae was significantly different between the two treatment groups (19% [placebo] vs. 9% [octreotide]; p=0.03). Overall, the incidence of complications was significantly more frequent among patients with pancreatic cancer than those with pancreatitis, independent of treatment (34.8% vs. 18.2%; p=0.01). Mortality was measured, but there was no significant difference between the treatment and placebo groups.

Friess et al (14) recruited 322 patients suffering from pancreatic or peri-ampullary tumours or from chronic pancreatitis. Patients were randomly assigned to receive three daily octreotide or placebo injections. Of the 322 randomized patients, only 246 were evaluable. Seventy-six patients were withdrawn because, intraoperatively, pancreatic resection was found to be impossible. Complication

rates were significantly lower for patients receiving octreotide versus placebo (32% vs. 55%; p<0.005). The difference between the groups was also statistically significant when only those with pancreatic or peri-ampullary tumours (38% [octreotide] vs. 65% [placebo]; p<0.01) were considered. Overall mortality within 90 days following surgery was measured in this RCT, but there was no evidence of any differences between the two treatment groups.

Update

As seen in Table 3, no statistically significant differences in complication rate, pancreatic fistula, or mortality were reported between treatment groups in the three randomized trials identified in the update of the literature (2u-4u).

Adverse Effects

Montorsi et al (12) reported two patients with nausea, two patients with vomiting, one patient with diarrhea, and one patient with prolonged postoperative bowel transit. Three of these patients received octreotide and three received placebo. Treatment was not discontinued in any of these patients.

Bassi et al (13) reported four patients with adverse effects related to octreotide treatment. One patient developed a skin rash and fever, and treatment was subsequently withdrawn. One patient developed a skin rash without fever, vomiting occurred in another patient, and biliary sludge in a third.

Update

In the three additional randomized trials identified (2u-4u), no adverse events directly related to treatment with octreotide were reported.

Interpretive Summary

Three randomized trials involving 843 patients have evaluated the use of octreotide for major pancreatic surgery (12-14). All three were multicentre, double-blind trials that included patients with pancreatic cancer, other peri-ampullary malignancies or pancreatitis. In each study, when all patients were analyzed, there was a significant decrease in complications in the octreotide group. In some studies, somewhat arbitrary criteria were used to categorize patients into low and high risk, which may not be applicable in all settings.

Based on these data, and the low cost and morbidity of octreotide therapy, octreotide should be commonly used in the perioperative management of patients undergoing major pancreatic resection.

Update

Data from the three randomized trials identified in the update are not consistent with three previously identified randomized trials. There are several differences within the body of evidence that serve to complicate the true treatment effect. These differences include variations in trial design, patient stratification and disease characteristics, surgical technique, octreotide timing, and outcome reporting. In the absence of further data, previous significant findings detected in favour of octreotide support the rationale for continued use as outlined in the original interpretive summary.

3. 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?

Results

Literature Search Results

Five randomized trials (15-19), one clinical practice guideline (5), and one systematic review of dose-titration data (20) were located and are eligible for review.

Because the randomized trials located for this indication included only patients with carcinoid syndrome, a literature search was performed to locate non-controlled trials of octreotide use in other neuroendocrine tumours. Non-controlled reports including only patients with carcinoid syndrome, or reports of trials where patients with carcinoid syndrome could not be separated from the results of patients with other neuroendocrine tumours were excluded. Fifteen non-controlled trials (21-35) were located and were considered eligible for review.

Outcomes

Randomized trials

All of the randomized trials of octreotide that were located included patients with carcinoid syndrome (15-19). Three trials were placebo-controlled (15-17), a fourth compared a short-acting subcutaneous formulation with different doses of the long-acting formulation (18), and the fifth trial compared octreotide with lanreotide, a long-acting somatostatin inhibitor (19). Symptom control was assessed in all trials, and quality of life was formally assessed in two trials (16,19). Survival was not assessed in any trial.

Saslow et al (15) randomized 12 patients with metastatic carcinoid disease to receive 50 µg of octreotide subcutaneously three times daily (n=6) or placebo (n=6). In order to assess gastric and small bowel transit, patients consumed a radiolabeled meal. Before and at 10-minute intervals after the meal, patients reported their symptoms of flushing and abdominal pain on a scale from 0 (no flushing or pain) to 10 (worst flushing and pain). Octreotide significantly reduced flushing during the first two hours after the meal, compared with placebo (0.2 vs. 0.9; p=0.03). There were no significant differences between the two study groups for abdominal pain scores. Octreotide was found to significantly retard overall colonic transit and proximal colonic emptying ($p<0.05$) when compared to placebo.

Jacobsen and Hanssen (16) reported a placebo-controlled, double-blind, cross-over study. Eleven patients with gastrointestinal neuroendocrine tumours and liver metastases were included, but only nine patients completed the study. Patients were treated for four weeks with 100 µg of octreotide administered twice daily and for four weeks with placebo in random starting order. Quality of life was assessed using the General Health Questionnaire (GHQ-30) and the Psychosocial Adjustment to Illness Scale (PAIS). Concentrations of 5-hydroxyindoeacetic acid (5-HIAA) were significantly reduced following octreotide compared to placebo (p=0.007). Flushing was significantly reduced for octreotide compared to placebo (20 vs. 32 episodes per week; p=0.01). The mean number of diarrhea episodes per week was also significantly reduced for octreotide (8 vs. 11; p=0.02). The scores from the GHQ-30 did not change significantly during therapy. Scores on the PAIS measuring the ability to relate socially and psychosocial distress were both significantly improved (p=0.03) following octreotide treatment. The authors reported on one patient who developed severe facial, leg, and arm edema with dyspnea when treated with octreotide. Treatment was discontinued. Another patient experienced severe nausea during the first four weeks of treatment; this patient left the study. Moderate degrees of headache, chest pain, abdominal discomfort and anxiety were reported, but more adverse effects were reported during the placebo period than the octreotide period.

Öberg et al (17) included 20 patients with carcinoid syndrome in a crossover trial of 50 µg of octreotide versus placebo. Patients received intravenous pentagastrin to induce a flush reaction. The subsequent flush reaction was graded on a 10-point visual analog scale. After placebo administration, 18 patients (90%) reported a flush reaction when given pentagastrin. The median flushing score was 8.5. After octreotide administration, 12 patients had a flushing reaction when given pentagastrin. The median flushing score was 2.0. All 20 patients had initial increased urinary 5-HIAA excretion. A median decrease in urinary 5-HIAA excretion of 26% was reported. Reported adverse effects following octreotide administration included gastric borborygmia and flatulence.

Rubin and colleagues (18) compared long-acting octreotide (LAR) at 10 (n=22), 20 (n=20), or 30 (n=25) mg every four weeks with open-label SC octreotide every eight hours (n=26) (dose not reported) in patients with a histologically confirmed diagnosis of carcinoid tumour with carcinoid syndrome. Assignment to the three doses of octreotide (LAR) was double-blind. Patients randomized to any one of the long-acting formulations continued to receive subcutaneous octreotide at their previous dosage until day 11, due to the time required to achieve therapeutic concentrations. Complete or partial treatment success, defined as symptomatic control on the long-acting arms with rescue medication needed on no more than two occasions, was comparable in each of the four arms (SC, 58.3% of patients; 10 mg, 66.7%; 20 mg, 71.4%; 30 mg, 61.9%). The median number of daily stools decreased significantly from baseline levels in all treatment groups and was similar across treatment groups. Flushing episodes were best controlled in the 20 mg LAR and SC octreotide groups.

The 10 mg LAR treatment was the least effective in the control of flushing. The only adverse effects that were considered related to octreotide treatment were abdominal pain in one patient, flatulence in two patients, nausea in three patients, and steatorrhea in one patient.

Thirty-three patients with carcinoid syndrome were included in a randomized crossover trial reported by O'Toole et al (19). Half of the patients received 200 µg of octreotide administered subcutaneously twice or three times daily for one month, followed by lanreotide 30 mg intramuscularly every 10 days for one month. The other half of the patients began treatment with lanreotide, followed by octreotide. Disappearance or improvement in flushes was reported in 68.0% of patients while on octreotide and 53.8% of patients while on lanreotide. Disappearance or improvement in diarrhea was reported in 50% of patients while on octreotide and 45.4% of patients while on lanreotide. A decrease greater than or equal to 25% in the 24-hour 5-HIAA level was observed in 50% of patients who received octreotide and 58% of patients who received lanreotide. Quality of life was assessed using the Nottingham Health Profile, which measures physical mobility, social isolation, pain, emotional reactions, energy, and sleep. There were no significant differences between the octreotide and the lanreotide groups with regard to quality-of-life scores. Mild episodes of abdominal pain and/or nausea and emesis were reported in 29% of patients receiving octreotide and in 14% receiving lanreotide.

Practice guideline from a consensus development panel

Harris and colleagues (5) established a consensus development panel to suggest guidelines for octreotide dose titration in patients with secretory diarrhea. Following a review of the available literature on patients with carcinoid tumours, the panel recommended that the initial dose and subsequent titration regimen of octreotide should depend on the condition of the patient. Patients with life-threatening symptoms should be given a 100 µg bolus intravenously, with subsequent intravenous doses of 50 µg every hour until stable. For patients with milder symptoms, an initial dose of 100 to 150 µg SC three times daily was recommended by the panel. The panel recommended an aggressive octreotide dose-escalation approach to ensure rapid and effective control of symptoms associated with carcinoid tumours. If the response to the initial dose of octreotide is determined to be insufficient, increasing the dose in 50 µg increments per dose up to 200 µg three times daily is recommended.

Dose titration data

An analysis of published dose titration data on octreotide by Harris and Redfern (20) revealed that maximum therapeutic doses effectively controlled symptoms of carcinoid tumours in up to 93% of patients. They recommend starting octreotide at 100 µg SC three times daily and titrating the dose in increments of 50 to 100 µg every eight hours until symptom control is achieved.

Non-controlled trials

The study descriptions and results of 15 single-arm trials of octreotide use in neuroendocrine tumours other than carcinoid tumours have been reported in Table 4. Tumour types included in these trials included glucagonomas, gastrinomas, insulinomas, VIPomas, Zollinger-Ellison syndrome (ZES), watery diarrhea syndrome (WDHA), and non-functioning tumours. A long-acting form of octreotide was used in one trial (21) while the other 14 delivered daily subcutaneous doses (22-35). One trial used a combination of octreotide and interferon (23).

Symptom responses were an endpoint in 11 trials (21,27-35). Patients in these trials reported improvement in pain (23,31,33,35), diarrhea (29,31,33-35), symptoms attributed to gastrinomas (27), glucagonomas (32), VIPomas (27), insulinomas (32), and other various symptoms attributed to neuroendocrine tumours.

Tumour response data was included in nine trials (21-24,26,28,30,32,34). Complete and partial responses were rarely observed (Table 4). Biochemical response data was included in 14 trials (21-23,25-35) and are outlined in Table 4.

Commonly reported adverse effects attributed to octreotide included pain, diarrhea, vomiting, steatorrhea, hyperglycemia, gallstones, and local skin irritation.

Table 4. Single-arm trials of octreotide in neuroendocrine tumours

First author, year (ref)	Octreotide dose and schedule	tumour types (N)	Symptom Response (% pts)	Tumour Response	Biochemical response
Tomassetti 2000 (21)	20 mg im q 4 wks LAR	glucagonoma (1) ZES/MEN-1 (2) non-functioning pancreatic (3)	abd pain (3 pts):CR 100% asthenia (3 pts): CR 100% necrolytic erythema (1pt): CR 100%	SD 83% PD 17%	ZES/MEN-1: decrease in gastrin levels in 2 pts glucagonoma: decrease in plasma glucagon in 1 pt
Angeletti 1999 (22)	500 µg/day sc	gastrinoma (4) non-functioning (3)	NR	(4 pts): PR 25% SD 75%	(4 pts) median decrease 66% in gastrin levels
Frank 1999 (23)*	200 µg tid + $5x10^6$ IU IFN tiw	gastrinoma (4) non-functioning (8)	NR	CR 8% SD 67% PD 25%	(4 pts): CR/PR 50%
Arnold 1996 (24)	200 µg sc tid (28 pts with PD 500 µg tid)	insulinoma (1) glucagonoma (4) gastrinoma (11) non-functioning (39)	NR	(32 pts): CR/PR 0% SD 25% PD 75%	NR
Bordi 1993 (25)	100 µg sc bid	ZES (5)	NR	NR	CR/PR 100%
Eriksson 1993 (26)	100 µg sc bid†	insulinoma (1) gastrinoma (3) non-functioning (6) WDHA (9)	NR	CR/PR 0% SD 32% PD 37%	CR/PR 31% (median duration 16 mos)
Cho 1990 (27)	100 µg	gastrinoma (3) VIPoma (2)	gastrinoma: CR/PR 67% VIPoma: CR/PR 100%	NR	gastrinoma: CR/PR 67% VIPoma: CR/PR 100%
Eriksson 1990 (28)	50-100 µg sc bid or tid	insulinoma (1) gastrinoma (3) WDHA (7) non-functional (3)	57% of pts improved symptomatically	CR/PR 0%	CR/PR 28% SD 22% PD 50%
Wynick 1989 (29)	50 µg sc bid then 500 µg sc tid	pancreatic endocrine (10)	diarrhea improved in 4 pts. skin rash resolved in 4 pts.	NR	CR/PR 70% SD/PD 30%
Eriksson 1988 (30)	50 µg sc bid	ZES (1), WDHA (6) insulinoma (1) non-functional (2)	CR/PR 70%	SD 100%	PR 40% SD 30% PD 30%
Vinik 1988 (31)	50 to 100 µg sc bid or tid	gastrinoma (8)	abd pain (7pts): CR 71% diarrhea (5pts): CR 100% nausea (3pts): CR 67% weight loss (3pts): CR 33% hematemesis (2pts): CR 100%	NR	CR/PR 100%
Kvols 1987 (32)	50 to 150 µg sc tid	glucagonoma (3) Insulinoma (4) gastrinoma (9) parathyroid (1) mixed (3), other (1) non-functional (1)	ZES (9 pts): CR 67% glucagonoma (3 pts): PR 33% insulinoma (4 pts): PR 75%	No evidence of tumour regression in any patient.	(21 pts) CR 67% PR 5% SD 10% PD 19%
Souquet 1987 (33)	100 µg sc bid	gastrinoma (7) glucagonoma (1) other (1)	diarrhea (4 pts): SD 100% pain (3 pts): PR 67%	NR	gastrinoma: CR 57%, PR 30%, SD/PD 14%, other (1 pt): PR 100%, glucagonoma (1pt): PR 100%
Ch'ng 1986 (34)	50 µg sc bid	VIPoma (2) glucagonoma (2) other (1)	diarrhea (2 pts): CR 100% rash (2 pts): CR 100%	PR 20% SD 60% PD 20%	PR 80% SD 20%
Wood 1985 (35)	50 µg sc bid	gastrinoma (2) mixed (2) VIPoma (2)	diarrhea (6 pts): CR/PR 83% pain (2 pts): CR 100%	NR	VIP (2 pts): PR 100% gastrin (4 pts): CR/PR 100% glucagon (2 pts): PR 100%

NOTES: bid = twice daily; CR = complete response; EPT = endocrine pancreatic tumour; IFN = interferon; im = intramuscularly; LAR = long-acting release; N = number; NR = not reported; PD = progressive disease; PR = partial response; pts = patients; q = every; sc = subcutaneous; SD = stable disease; tid = three times daily; tiw = three times weekly; VIP = vasoactive intestinal polypeptide; WDHA = watery diarrhea syndrome; ZES/MEN –1 = Zollinger-Ellision syndrome associated with multiple endocrine neoplasia type 1

*Median duration of response was 7 months in patients with gastrinoma, 12 months in patients with non-functioning tumours

† Two patients receiving high-dose continuous sc infusions of octreotide (> 3000 µg/day)

Interpretive Summary

The results of the five, small, randomized trials indicate that octreotide is effective in controlling flushing and diarrhea associated with carcinoid syndrome. Octreotide significantly reduced episodes of flushing and diarrhea in two of the trials of octreotide versus placebo (15,16). The dosages of the immediate-acting formulation of octreotide in these two trials ranged from 150 µg/day (15) to 200 µg/day (16). A small pharmacodynamic study (17) reported a decrease in pentagastrin-induced flushing and 5-HIAA urinary excretion with octreotide administered in a 50 µg dose. Another small comparative clinical trial (19) reported similar efficacy with subcutaneous octreotide and a longer 10-day acting peptide (lanreotide) in controlling carcinoid symptoms.

The results of the RCT by Rubin et al (18) investigating the efficacy of a long-acting formulation of octreotide indicate that this formulation is as effective as three-times-daily subcutaneous octreotide in controlling the symptoms associated with carcinoid syndrome. However, further studies should be performed to confirm this effect. For immediate relief of symptoms, subcutaneous administration of short-acting octreotide is likely to be required during initiation of treatment with long-acting octreotide.

The body of reviewed evidence supports the efficacy of octreotide in the control of symptoms of carcinoid tumours. Non-controlled studies in other neuroendocrine tumours suggest that symptoms associated with hormonal secretion can be improved with octreotide. In patients with carcinoid syndrome, it is recommended that octreotide be administered 100 µg SC three times daily or 200 µg twice daily, with an increase in dose of 50 to 100 µg every eight or twelve hours until symptom control is achieved.

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?

Treatment of patients with inoperable bowel obstruction typically consists of the placement of a nasogastric tube and liquid supplementation. Octreotide has been shown to reduce gastrointestinal secretions, which could potentially avoid the use of a nasogastric tube or allow a tube already in place to be removed.

Results

Literature Search Results

Two small, randomized trials involving only 35 patients comparing octreotide to hyoscine butylbromide (36) or scopolamine butylbromide (37) in cancer patients with chronic bowel obstruction were located and are eligible for review. These two trials, along with three single-arm studies, including a total of 51 patients (38-40), are shown in Table 5. The trials report on control of nausea and vomiting, use of nasogastric tubes, quantity of gastrointestinal secretions, and other measures of efficacy. Quality of life was not assessed in any of the studies.

Update

One additional randomized trial (5u) was identified in the updated search of the literature (Table 3).

Outcomes

Mercadante et al (36) randomized 18 patients with inoperable bowel obstruction to receive octreotide or hyoscine butylbromide. Only 15 patients were evaluable, as three patients died before an appropriate evaluation was done. No patient had a nasogastric tube. Significant differences in mean episodes of vomiting between the two groups were reported at 24 hours (1.3 [octreotide] vs. 4.3 [butylbromide]; p=0.01) and 48 hours (0.4 vs. 2.8; p=0.004). Significant differences in mean episodes of nausea between the octreotide group and the butylbromide group were reported at 48 hours (0.4 vs. 1.7; p=0.02) and 72 hours (0.5 vs. 1.6; p=0.03), respectively. Continuous pain values were significantly lower in the octreotide group at baseline, 24 hours and 48 hours.

Ripamonti et al (37) randomized 17 patients with a nasogastric tube to receive either octreotide or scopolamine butylbromide for three days. There was a significant reduction in nasogastric tube secretion in patients treated with octreotide at 24 hours (p=0.016) and at 48 hours (p=0.020)

compared to baseline secretion values. No significant secretion reductions were noted at any time point in patients receiving scopolamine butylbromide. Removal of the nasogastric tube was possible in 13 patients (7 receiving octreotide). Both octreotide and butylbromide were found to significantly reduce continuous as well as colicky pain compared to baseline values; no significant differences were observed between the two groups. Nausea intensity at 24 hours was significantly lower in patients treated with octreotide compared to patients treated with butylbromide (p=0.05).

The case series study reported by Mangili et al (38) involved 13 terminal ovarian cancer patients. Eight of these women had nasogastric tubes. Octreotide was found to control vomiting due to bowel obstruction in all cases, with complete relief of symptoms in three days. In the eight patients with nasogastric tubes, the mean initial production of nasogastric drainage was 1687.5 ml/day. Nasogastric tubes were removed when the drainage decreased to below 50 ml/day and the patient achieved complete relief from vomiting. Eight patients were discharged from the hospital and treated at home with octreotide. The mean survival from the diagnosis of obstruction was 27.1 days.

In the phase I/II trial reported by Khoo et al (39), 24 patients with advanced cancer received octreotide in varying doses, and 14 (58%) experienced complete control of nausea and vomiting. An additional four patients (17%) showed a partial response to octreotide, defined as nausea or transient vomiting. Nasogastric aspirate was reduced in varying degrees in the five patients who had nasogastric tubes.

Mercadante et al (40) studied 14 patients with advanced cancer no longer responsive to anti-tumour treatment. Three of the 14 patients had nasogastric tubes. The mean survival time from diagnosis of bowel obstruction was 17.5 days. Octreotide controlled vomiting in 12 patients. In two additional patients, vomiting was reduced but not completely controlled. Octreotide controlled symptoms and allowed for the removal of a nasogastric tube in two out of three patients.

Update

Mystakidou et al (4u) randomized 68 patients with inoperable bowel obstruction to receive octreotide or hyoscine butylbromide. Significant differences in favour of octreotide over hyoscine butylbromide were reported 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.

Table 5. Studies of octreotide for chronic bowel obstruction in advanced malignancies.

Author year (ref.)	Population	No. pts	Treatment	Outcomes of Interest
Randomized Trials				
Mercadante 2000 (36)	GI Ovarian Breast	9 6	Octreotide 300 µg/d SC infusion (0.3 mg/d) Hyoscine butylbromide 60 mg/d SC	episodes of vomiting, amount of fluids administered, nausea, drowsiness, dry mouth, pain
Ripamonti 2000 (37)	GI Ovarian Breast	9 8	Octreotide 300 µg/d SC infusion (0.3 mg/d) for 3 d Scopolamine butylbromide 60 mg/d SC for 3 d	pain, nausea, dry mouth, drowsiness, quantity of GI secretions, fluids administered
Update				
Mystakidou 2002 (4u)	GI Abdomen Pelvis	34 34	Octreotide 600-800 µg/d SC infusion Hyoscine butylbromide 60-80 mg/d SC	nausea, vomiting, fatigue, anorexia, pain
Non-controlled Trials				
Mangili 1996 (38)	Ovarian	13	Octreotide 300-600 µg/d SC bolus or IV continuous infusion	mean survival, control of vomiting, nasogastric drainage
Khoo 1994 (39)	GI Ovarian	24	Octreotide 150-1200 µg/d SC continuous infusion	control of nausea and vomiting, volume of nasogastric aspirate
Mercadante 1993 (40)	GI Ovarian Sarcoma	14	Octreotide 300-600 µg/d SC bolus or continuous infusion	episodes of vomiting, pain, side effects of octreotide

Note: d = day; GI = gastrointestinal, IV = continuous intravenous infusion; No. = number of pts = patients; SC = subcutaneous injection.

Adverse Effects

Mangili et al (38) reported no important side effects related to octreotide treatment. Mercadante et al (40) reported pain at the injection site in 50% of the patients and an uncomplicated skin reaction in one patient. Khoo et al (39) reported no adverse effects due to treatment with octreotide.

Interpretive Summary

Although these were small studies, the data from the two available, randomized trials suggest superior symptomatic relief for octreotide compared with butylbromide, in terms of nausea, vomiting, and pain (36), and nasogastric tube secretions and nausea (37). The non-controlled studies also indicate that the use of octreotide can decrease symptoms associated with chronic bowel obstruction and eliminate the need for a nasogastric tube in some patients. There are no randomized trials available that compare quality of life with and without octreotide.

Update

New data are consistent with the findings of the previously identified randomized trials.

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?

Results

Literature Search Results

Nine randomized trials have been located that have investigated the anti-tumour effects of octreotide (41-49). Three randomized trials have investigated the activity of octreotide in women with metastatic breast cancer (41-43) and six studies (two published in abstract form only) have investigated the activity of octreotide in patients with advanced gastrointestinal cancers (44-49). The studies are described below and the results are presented in Table 6

Update

One small randomized trial comparing octreotide to placebo control for patients with advanced liver cancer was identified in the update of the literature (6u).

Table 6. Randomized trials of octreotide for the treatment of advanced malignancies.

First author, year (ref.)	No. of Pts.	Tumour Primary Site	Oct. Dose	Treatments	Objective Response (%)	Median Time-to-Prog. (weeks)	Median Survival (weeks)	Octreotide Side-Effects*
Bajetta 1999 (41)	99 100	Breast (advanced)	160 mg im LAR	Octreotide + tam Tam + placebo	20% 21%	25 27 p=0.62	NR NR	D = 53% N = 16% AC = 11%
Ingle 1999 (42)	67 68	Breast (advanced)	150 µg TID sc	Octreotide + tam Tam	43% 49% p=0.70	44 61 p=0.26	NR NR p=0.92	D = 36% ST = 9% N = 36%
Bontenbal 1998 (43)	10 12	Breast (advanced)	200 µg TID sc	Octreotide + tam + nor Tam	55% 36%	84 32	NR NR	NR
Burch 2000 (44)	42 44	Pancreatic (advanced)	500 µg TID sc	Octreotide 5-FU + or - leucovorin	NR NR	6 15 p=0.01	17‡ 29‡ p=0.80	D = 2% N = 2%
Kouroumalis 1998 (45)	28 30	Liver (advanced)	250 µg BID sc	Octreotide No treatment	NR NR	NR NR	56 17 p=0.0024	D = 40%
Pederzoli 1998 (46) [abstract]	93 92	Pancreatic Stage II-IV	LAR	Octreotide Placebo	0% 0%	NR NR	16 17 p=0.744	NR
Roy 1998 (47) [abstract]	284	Pancreatic Stage II-IV	LAR	Octreotide + 5-FU Placebo + 5-FU	NR NR	NR NR	23 22 p=0.649	NR

Cascinu 1995 (48)	55 52	Stomach Pancreas Colorectal (advanced)	200 µg TID sc	Octreotide BSC	0% 0%	26 22	20 11 p<0.0001	D= NR ST = 18% HBS =36% AC = 5%
Goldberg 1995 (49)	131 129	Colon (advanced)	150 µg TID sc	Octreotide None or placebo	2% 1%	15 14	73 72	D = 44% ST = 30% N = 26%
Update								
Yuen 2002 (6u)	35 35	Liver (advanced)	250 µg BID sc + LAR	Octreotide Placebo	NR NR	NR NR	8 8	NR

NOTES: BID = twice daily; BSC = Best Supportive Care; im = intramuscularly; LAR = long acting octreotide; No. = number of; NR = not reported; Oct. = octreotide; sc = subcutaneously; TID = three times daily, except in Cascinu trial where given for 5 days of each week
*Octreotide side effects: AC = abdominal cramps; C = cholecystectomy; D = diarrhea; G = gallstones; GS = gallbladder symptoms; HBS = high blood sugar; N = nausea; ST = steatorrhea; Tam = tamoxifen; Nor =Norprolac
† Patients may also have been receiving doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days for four cycles at the discretion of the physician.
‡ Estimated from survival curves.

Outcomes

Metastatic breast cancer

Three randomized trials of octreotide in metastatic breast cancer are available for review (41-43). Two of the trials investigated octreotide administered in three daily doses (42,43), and one used a long-acting form of octreotide administered once monthly (41).

In the trial reported by Bajetta et al (41), 199 patients with metastatic breast cancer were randomized to receive either octreotide (160 mg im every two weeks for two months and then every four weeks) and tamoxifen, or tamoxifen and placebo.

The trial by Ingle et al, in collaboration with the North Central Cancer Treatment Group (NCCTG) and the Mayo Clinic (42), allocated 135 post-menopausal women with progressive metastatic breast cancer to receive 20 mg/day of tamoxifen alone or combined with 150 µg of octreotide administered three times daily.

In the study by Bontenbal et al (43), 22 post-menopausal women with previously untreated metastatic breast cancer were randomized to receive either tamoxifen 40 mg/day alone, or the same dose of tamoxifen plus octreotide 200 µg three times daily and the anti-prolactin drug CV 205-502 (Norprolac) 75 µg/day.

Response rates were reported in three trials (41-43) (Table 2). Only one trial provided a p-value, which was non-significant (42). Median time-to-progression was also reported in all three trials (41-43); no significant differences were detected in the two trials that provided p-values (41, 42). Survival data were available from one trial (42). Ingle et al reported a mortality hazard ratio (tamoxifen vs.. tamoxifen plus octreotide) of 0.98 (95% CI, 0.62 to 1.55; p=0.92). The trial reported by Bajetta et al was terminated at the interim analysis, as there was no possibility of increased efficacy in combining long-acting octreotide with tamoxifen (41).

Advanced gastrointestinal cancers

Six randomized trials have investigated the use of octreotide for various gastrointestinal cancers (44-49). Four of these studies (one published in abstract form only) have compared octreotide to best supportive care (48), no treatment (45), or placebo (46,49). A fifth trial compared octreotide to chemotherapy with 5-fluorouracil (5-FU) with or without leucovorin (44). The sixth trial, available in abstract form only, compared 5-FU and octreotide to 5-FU and placebo (47). Two trials used a long-acting formulation of octreotide (46,47), while the rest used multiple daily subcutaneous injections.

Objective response rates were reported in three trials involving a total of 552 patients (46,48,49); no significant differences were reported in any of the individual trials. Median time-to-progression was also reported in three trials involving a total of 453 patients (44,48,49). Burch et al reported a significant prolongation of median time-to-progression in patients with advanced pancreatic cancer who received 5-FU or 5-FU combined with leucovorin versus octreotide (15 weeks vs. 6 weeks; p=0.01) (44). No other significant differences in time-to-progression were reported.

Median survival was reported in all six trials involving a total of 980 patients (44-49). Patients with hepatocellular carcinoma receiving octreotide in the study reported by Kouroumalis et al (45) showed a significant improvement in median survival (56 vs. 17 weeks; p=0.0024), as well as overall survival at six months (75% vs. 37%) and 12 months (56% vs. 13%), compared with patients who received no treatment. In the trial by Cascinu et al (48), patients with advanced stomach, pancreatic, or colorectal cancers who received octreotide had a significantly longer median survival (20 vs. 11 weeks; p<0.0001) than patients who were randomized to receive only best supportive care (Table 2). Patient accrual in the trial reported by Burch et al (44) was terminated after 84 patients with advanced pancreatic cancer were evaluated. Time-to-progression and survival were found to be inferior in the octreotide arm compared with chemotherapy. Similarly, accrual was terminated in the study by Goldberg et al (49) because, when 260 eligible patients with advanced colon cancer were randomized, the observed survival for the patients receiving octreotide was no better than that of the patients in the control group when half of the anticipated deaths had been observed.

Kouroumalis et al (45) reported that quality of life was enhanced by octreotide as indicated by improved appetite in 86% of patients, improved body weight in 43% of patients. and improved feeling of well being in 54% of patients.

Update

Yuen et al (6u) did not detect any survival difference with long-acting octreotide versus no further treatment for patients with advanced hepatocellular carcinoma.

Adverse Effects

Side effects of octreotide treatment were recorded in most of the trials (Table 2). Common complaints included nausea, diarrhea, vomiting, steatorrhea, and abdominal cramps.

In the trial by Bontenbal et al (43), 40-50% of potentially eligible patients with advanced breast cancer refused randomization because of the three daily injections. In the trial by Ingle et al (42), 22% of patients with advanced breast cancer receiving tamoxifen and octreotide reduced, stopped, or did not comply with the octreotide treatment regimen. Seven patients discontinued treatment because of gastrointestinal complaints (four cases), weight loss and anorexia (one case), severe hot flushes (one case), and refusal (one case). Three patients reduced their octreotide dose because of diarrhea (two cases) and musculoskeletal pain (one case). In the trial by Goldberg et al (49), the dose of octreotide was reduced in 5% of patients because of diarrhea and steatorrhea. Kouroumalis et al (45) reported that four patients discontinued treatment because of the required twice-daily injections of octreotide.

Interpretive Summary

In advanced breast cancer patients, the benefits observed in the early, incomplete, small trial by Bontenbal et al (43) have not been confirmed by the two larger trials by Ingle et al (42) and Bajetta et al (41). The patient populations were similar, but there were differences in the drugs and dosage used. However, these were not felt to explain the lack of benefits in the two most recent trials (41,42). Therefore, we cannot recommend the use of octreotide in the management of advanced breast cancer. These results do not preclude the possibility that octreotide may be active in the adjuvant setting in breast cancer. Two randomized trials reported as abstracts, the NSABP B-29 (50) and CAN-NCIC-MA-14 (51), may provide further information about octreotide activity in an adjuvant setting. However, it should be noted that both studies were terminated early because of an increased incidence of adverse events (gallbladder toxicity), which may limit the statistical power for survival outcomes.

In patients with advanced gastrointestinal cancers, the small trial by Cascinu et al (48) found a significant survival and palliative effect in patients with pancreatic, gastric, and colorectal cancer. These results have not been confirmed by four other disease-specific trials, two of which were substantially larger (44,46,47,49). Goldberg et al (49) investigated 260 asymptomatic advanced colon cancer patients and did not detect a survival advantage for patients treated with octreotide. Three other trials investigated patients with unresectable pancreatic cancer (44,46,47). None of the trials demonstrated an advantage for octreotide treatment. In view of the conflicting findings regarding octreotide activity in advanced colon and pancreatic cancer, we cannot recommend its use for these

conditions. It is clear from the above trials that important considerations in the design of future trials are disease-site specificity and use of placebo controls.

It is noteworthy to mention separately the trial of Kouroumalis et al (45) involving patients with hepatocellular carcinoma. These investigators found significant palliative and anti-tumour effects rarely observed with other systemic therapies in this disease in patients treated with octreotide. These findings, in a disease with an otherwise dire prognosis, should stimulate further trials of octreotide, possibly using its long-acting formulation.

Update

The small trial by Yuen et al (6u) did not detect any significant survival benefit with octreotide in patients with advanced hepatocellular carcinoma.

V. ONGOING TRIALS

The Systemic Treatment DSG is aware of the following ongoing trials evaluating the use of octreotide in patients with cancer:

URCC-CCC-01-16 URCC-CC-1202, URCC-U0116, NCI-P02-0233: Phase III Randomized Study of Octreotide versus Standard Care for Chemotherapy-Induced Diarrhea in Patients with Colorectal Cancer**.** A randomized, open-label, multicenter study with a total of 626 patients (313 per treatment arm) to be accrued. This summary was last modified in March of 2004.

E-E1295, NCI-P97-0081, CLB-9770, SWOG-E1295: Phase III Randomized Trial of Octreotide Acetate vs Conventional Therapy with Loperamide Hydrochloride for Chemotherapy Related Diarrhea in Patients with Colorectal Cancer A randomized, open-label, multicenter study with a total of 500 patients to be accrued. This summary was last modified in 08/2000.

NU-97XI, NCI-G00-1685: Phase II study of octreotide as palliative therapy for inoperable bowel obstruction secondary to cancer. A total of nine to 25 patients with inoperable bowel obstruction secondary to cancer or metastatic or primary abdominal cancer will be accrued for this study. The objective of the study is to determine the effectiveness of octreotide in the palliation of bowel obstruction secondary to cancer and to characterize the dose and tolerability of octreotide in this patient population. This summary was last modified in March of 2000.

VI. DISEASE SITE GROUP CONSENSUS PROCESS

When octreotide was first considered as a guideline topic for the Systemic Treatment DSG, five different indications for the drug in patients with cancer were discussed. Data were available on the use of octreotide as an anti-tumour agent, in chemotherapy-induced diarrhea, in pancreatic surgery, in neuroendocrine tumours, and for chronic bowel obstruction. The group decided to combine all the indications for octreotide into one single report, rather than producing a separate report for each of the various indications.

A preliminary literature search was conducted to locate randomized trials for each of the above-mentioned indications. The amount and quality of the data located varied for each indication. For the neuroendocrine tumour section, the only randomized data involved patients with carcinoid tumours. The group wanted to know if there was any evidence that octreotide was active in other neuroendocrine tumours, and so another literature search was performed to locate non-randomized trials of octreotide use in non-carcinoid neuroendocrine tumours. At the time that the first literature search was conducted, there were no randomized trials available on the use of octreotide in chronic bowel obstruction. The group decided to conduct a search for reports of non-randomized trials for this indication and to provide a summary of the evidence but to make no actual recommendations for this section. Since that time, two small, randomized trials have been published on the use of octreotide in chronic bowel obstruction, and the group decided to make a recommendation for this section. Members of the Systemic Treatment DSG agreed with the recommendations that were developed for the other sections of the guideline.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Systemic Treatment DSG drafted the following recommendations:

Treatment of Chemotherapy-Induced Diarrhea

Target Population

These recommendations apply to adult cancer patients receiving chemotherapy including 5-FU and/or cisplatin who have developed diarrhea sufficiently profuse to put them at risk for dehydration.

Key Recommendations

- A reasonable initial treatment approach to chemotherapy-induced diarrhea is standard anti-diarrheal agents in the usual approved doses (generally NCI-CTC grade 3/4).
- If the diarrhea has not substantially improved in 24 hours, or if the patient requires intravenous rehydration, then octreotide can be considered, beginning at a dose of 100 µg subcutaneously three times daily and escalated every eight hours by 50 to 100 µg until the diarrhea is controlled, to a maximum of 500 µg three times daily (e.g. loperamide 4 mg initially, then 2 mg after every unformed stool and until there has been no diarrhea for 12 hours up to a maximum of 16 mg/day).

Qualifying Statements

- For practical purposes and patient convenience, oral anti-diarrheal agents are used for the initial treatment of chemotherapy-induced diarrhea. For diarrhea unresponsive to oral agents, parenteral octreotide is preferred.

Future Research

- The mechanism of diarrhea in patients receiving chemotherapy with CPT-11 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.

Octreotide Following Pancreatic Surgery

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, should be part of the standard management for patients undergoing pancreatic surgery.

Symptom Relief of Carcinoid and Other Neuroendocrine Tumours

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.

Future Research

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

Octreotide Use in Patients with Chronic Bowel Obstruction

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 (0.3 mg) 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.

Anti-tumour Effects of Octreotide in Advanced Malignancies

Target Population

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

Recommendations

- Octreotide cannot be recommended as an anti-tumour agent for the treatment of metastatic breast cancer, advanced pancreatic cancer, 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.

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.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 152 practitioners in Ontario (141 medical oncologists and eleven surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

Results

Key results of the practitioner feedback survey are summarized in Table 7. Of the 141 medical oncologists, seventy-eight (55%) returned a survey. An average of 47 (61%) respondents indicated that the practice guideline report was relevant to their clinical practice, and they completed the survey. Of the eleven surgeons, seven (55%) returned a survey, and 6 (86%) respondents indicated that the practice guideline report was relevant to their clinical practice and completed the survey. A small number of questionnaires were returned with checkmarks to indicate responses as opposed to the required numerical values. These checkmarks were inferred as "agree" responses.

Table 7. Practitioner responses to eight items on the practitioner feedback survey.

	Octreotide as an anti-tumour agent	Octreotide in chemotherapy induced diarrhea	Octreotide following pancreatic surgery	Octreotide for symptom relief in neuroendocrine tumours	Octreotide for relief of chronic bowel obstruction
Item	**Number (%) of practitioners who responded strongly agree or agree with survey items**				
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	39 (93%)	41 (100%)	6 (100%)	30 (100%)	35 (97%)
There is a need for a clinical practice guideline on this topic.	35 (81%)	40 (98%)	5(83%)	30 (97%)	36 (100%)
The literature search is relevant and complete.	38 (95%)	44 (100%)	5 (83%)	30 (100%)	34 (94%)
The results of the trials described in the report are interpreted according to my understanding of the data.	41 (98%)	42 (98%)	6 (100%)	29 (97%)	34 (94%)
The draft recommendations in this report are clear.	42 (100%)	43 (100%)	6 (100%)	30 (100%)	36 (100%)
I agree with the draft recommendations as stated.	42 (100%)	41 (95%)	6 (100%)	30 (100%)	34 (94%)
This report should be approved as a practice guideline.	37 (90%)	39 (93%)	5 (83%)	30 (100%)	33 (92%)
	Number (%) of practitioners who responded very likely or likely with survey item				
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	28 (74%)	32 (78%)	5 (83%)	27 (82%)	31 (80%)

NOTE: Some percentages do not add to 100 because of missing data

Summary of Main Findings

Seventeen (22%) respondents provided written comments. The main points were:

1. *Octreotide as an anti-tumour agent*:
   - One practitioner remarked that the recommendation should state that octreotide in unresectable hepatoma is supported by a small randomized trial.
   - Two practitioners commented that recommendations were of uncertain necessity as octreotide is not commonly used for the specified indications.
   - One practitioner found the discussion of results in the interpretative summary to be confusing.
2. *Octreotide in chemotherapy-induced diarrhea:*
   - One practitioner questioned why a dose-escalation study was excluded from the meta-analysis when the draft recommendation goes on to state that octreotide can be increased to a maximum 500 µg tid.
   - One practitioner commented that the recommendations for use of octreotide do not seem to reflect the data that was summarized, i.e. that value or cost judgements were made in recommending loperamide initially.
3. *Octreotide in pancreatic surgery:*
   - One practitioner remarked that a large randomized trial by the Hopkins group may have been missed in the literature search
4. *Octreotide in neuroendocrine tumours:*
   - One practitioner commented that the dose of octreotide may exceed 800mg subcutaneously

every eight hours, and caution should be exercised in recommending an upper dose limit. The practitioner also noted that often after treatment with radiopharmaceuticals, a considerably higher dose is administered intravenously and then subcutaneously for 4-6 weeks.

5. *Octreotide in chronic bowel obstruction*
    - One practitioner commented that the placement of a nasogastric tube is a superior method for symptomatic relief as patients can continue to eat and drink provided that the bore of the tube is large, and there is no need for daily injections, no local pain, and no huge costs to pharmacy
    - One practitioner questioned whether the studies of bowel obstruction used subcutaneous infusions or could the same effect be gained by subcutaneous injections.

Modifications/Actions

1. *Octreotide as an anti-tumour agent*:
    - The small randomized trial of hepatoma was mentioned in the Key Evidence and Future Research sections. While there is evidence for activity in this setting, the results presented must be considered preliminary. No modifications were made to the guideline.
    - While the recommendations may be of uncertain necessity, the role of octreotide as an anti-tumour agent is of clinical interest and warrants investigation. However, to address these comments, this section was re-positioned in the document to become the last of the five clinical questions of interest.
    - A section of the interpretative summary was reworded to improve clarity.
2. *Octreotide in chemotherapy induced diarrhea:*
    - As previously addressed in the text, the dose escalation study was too dissimilar from the three randomized trials to be included in the meta-analysis. This study however, supports that escalation to 500µg sc tid is reasonable if control is not achieved with initial starting doses of 100µg sc tid.
    - The recommendation of loperamide as an initial treatment over octreotide in chemotherapy-induced diarrhea was revised to provide greater clarity. As a result, the qualifying statement was also removed from this section.
3. *Octreotide in pancreatic surgery:*
    - The trial from the Hopkins Group by Yeo et al (3u) was included in an update of the literature.
4. *Octreotide in neuroendocrine tumours:*
    - While recommendations from a consensus development panel recommend an upper dose limit with octreotide, the Systemic Therapy DSG agreed that an upper dose limit not be recommended. No modifications were made to the guideline.
5. *Octreotide in chronic bowel obstruction*
    - The available data supports that octreotide, in patients with or without nasogastric tubes, provides symptomatic relief in terms of nausea, vomiting, pain, and nasogastric tube secretions. No modifications were made to the guideline.
    - Greater information on the delivery of octreotide was added to Table 6.

Practice Guidelines Coordinating Committee Approval Process

Results

The practice guideline report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Ten members of the PGCC returned ballots. Seven members approved the practice guideline report as written. Two members provided suggestions for consideration, and one member approved the report conditional upon a re-wording of one of the recommendations.

Modifications/Actions

Based on the comments of the members of the PGCC, The Systemic Treatment DSG addressed the minor comments and suggestions, and revised one of the recommendations to better reflect the evidence reviewed.

VIII. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Systemic Treatment DSG.

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 trials identified in an update of the literature did not detect any significant differences in serious complications or in 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

- In one trial, significant differences in favour of octreotide over hyoscine butylbromide were reported 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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Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T. Role of octreotide in the management of patients with cancer. *Curr Oncol* 2003;10(3):161-79.

X. ACKNOWLEDGEMENTS

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For a full list of members of the Systemic Treatment Disease Site Group and the Practice Guidelines Coordinating Committee, please visit the CCO Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. National Cancer Institute common toxicity criteria – diarrhea.

Adverse Event	Grade				
	0	1	2	3	4
Diarrhea – patients without colostomy	none	increase of <4 stools/day over pretreatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Diarrhea – patients with a colostomy	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
Diarrhea associated with graft versus host disease (GVHD) for BMT studies, if specified in the protocol.	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For pediatric BMT studies, if specified in the protocol.		>5 - ≤10mL/kg of diarrhea/day	>10 - ≤15mL/kg of diarrhea/day	>15mL/kg of diarrhea/day	

Source: Cancer Therapy Evaluation Program. Common toxicity criteria version 2.0. April 30, 1999. Available at: http://ctep.info.nih.gov/CTC3/ctc.htm. Accessed October 24, 2000.

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The Role of Octreotide in the Management of Patients with Cancer
Guideline Review Summary

Review Date: December 2012

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2003, and updated in 2004. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (YM) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be archived. The Systemic Treatment Guideline Development Group (GDG) archived the recommendations found in the summary section in December 2012.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

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?

Literature Search and New Evidence

The new search (July 2004 to May 2012) yielded 13 references representing 11 RCts and 2 non controlled trials were found. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The Systemic Treatment GDG **ARCHIVED** the 2003 recommendations on The Role of Octreotide in the Management of Patients with Cancer. Therefore this guideline will no longer be maintained by the PEBC. The GDG will decide if and when a new guideline in this topic area will be produced.

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Document Review Tool

Number and title of document under review	12-7 The Role of Octreotide in the Management of Patients with Cancer
Current Report Date	May 7, 2003
Clinical Expert	Dr. Yolanda Madarnas
Research Coordinator	Chika Agbassi
Date Assessed	Sept 2011
Approval Date and Review Outcome (once completed)	11 December 2012 (ARCHIVED)

Original Question(s):

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?

Target Population for questions

1. 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).
2. These recommendations apply to patients undergoing pancreatic surgery for pancreatic cancer.
3. 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).
4. These recommendations apply to terminally ill cancer patients with inoperable bowel obstruction.
5. These recommendations apply to patients with metastatic breast cancer, advanced colorectal, stomach, or pancreatic cancer, or unresectable malignant hepatoma.

Study Section Criteria:

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Randomized trials comparing octreotide with placebo, observation, or other treatment in cancer patients for the indications mentioned in the guideline questions.
- Non-controlled reports of octreotide were considered only for questions three (neuroendocrine tumours) and four (chronic bowel obstruction).
- Outcomes of interest, including tumour response, survival, symptom relief or control, and quality of life were reported.

Exclusion Criteria

- Letters and editorials were not considered.
- Papers published in a language other than English were not considered

Search Details:

- July 2004 to May 2012 (Medline wk 4 + wk 52 Embase)
- July 2004 to July 2012 (ASCO Annual Meeting)

Brief Summary/Discussion of New Evidence:

Of 1326 total hits from Medline + Embase and 30 total hits from ASCO conference abstract searches, 13 references representing 11 RCTs and 2 non controlled trials.

Interventions	Name of RCT (med F/U)	Population (n)	Outcomes	Brief results	References
Octreotide in Diarrhea control					
Octreotide LA R 30mg IM vs Physician's treatment of choice	LARCID	Colorectal Ca (193)	CID, QoL	Octreotide did not show any significant benefit over physician's choice of treatment.	Hoff P et al 2012 [ABSTRACT]
Prophylactic LA Octreotide 30mg IM → 2nd dose on d22 (±3d) of RT vs Placebo	RTOG trial 0315 (9.64mos)	Anorectal Ca on CT & RT (233)	*CID QoL	There was no significant difference in the incidence of diarrhea and QoL between arms.	Zachariah B. et al 2010
Octreotide 100µg SC on d1 → Depot octreotide IV on d2, and d29 Vs placebo	N00CA	(n=125)	CID AC	There was no significant difference between arms	Martenson JA. et al 2008
Octreotide LAR 30mg x6doses vs LA Octreotide 30mg x6doses	STOP Trial	(n=147)	*CID IV hydration	There wasno significant difference between arms	Rosenoff SH. et al 2006 [ABSTRACT]
OCTREOTIDE use in pancreatic cancer surgery					
Octreotide 0.1mg SC qd x7d Vs No treatment		Age 16-86yrs (n=105)	Pancr fistula, hospital stay	There was no significant difference between arms	Hess UJ. et al 2005
Octreotide in NET and Carcinoid Syndrome					
**Octreotide LAR		GEP-NET Ave Age 61yrs (93)	QoL	NET patients treated with octreotide reported improvement in global health and diarrhea	Gyökeres T et al 2012 [ABSTRACT]
Octreotide LAR 30mg qMos x18mos Vs Placebo		KPS >60 (n=85)	TTP	Octreotide was significantly better than placebo with a median TTP of 14.3mos against 6mos (HR: 0.34; 95% CI: 0.20–0.59) *P*=0.000072	Arnold R et al 2009 [ABSTRACT]
Octreotide in advanced/metastatic CA					
**Octreotide 300µg/d	NCCTG	Terminally ill BO (n=43)	OIR, QoL AP, AD, N/V,	Compared to baseline, octreotide significantly improved AP (P=0.009), AD , NV, fatigue thirst and anorexia (p=0.001).	Hisanaga T. et al 2010
Octreotide LAR 30mg IM q4W x 2yrs vs placebo		HCC Age≥18yrs (272)	OS,PFS	There was no significant difference between arms	Barbare J. et al 2009
Octreotide LAR 30mg qmos +Tamoxifen 30mg qd Vs Tamoxifen 30mg qd		HCC KPS >60% (109)	Survival TR, QoL	There was no significant difference between arms.	Verset G. et al 2007
Octreotide 0.5mg sc q8h x6W → LA Octreotide 20 mg IM @ W4-8 → LA Octreotide 30 mg IM @ W12 → LA Octreotide 30 mg IM q4W vs Placebo		HCC Stage A-B KPS >60% (109)	Survival QoL	Survival time was significantly higher in the octreotide group; 49W against 28W in the placebo arm. P=<0.01 Based on the first 12M, octreotide arm showed a 22% decrease in QLQ-C30 score against 39% in the placebo arm. P< 0.05.	Dimitroulopoulos et al 2007
octreotide LAR 30 mg IM q4W vs Placebo	HECTOR	Untreated HCC >6mos (120)	Survival	Compared to placebo, there was no significant survival benefit for HCC patients treated with octreotide.	Becker G et al 2007
Octreotide 20 mg IM q4W + Dexamethasone 4mg qd x 1mos gradually reduced to 1mg by 4 mos		AARPC Stage D_3 (n=38)	PFS,OS	PFS (7mos vs. 1mos , p<0.0001) and OS (12mos vs. 9mos, p<0027) were significantly better in the octreotide arm.	Mitsiades CS. et al 2006

→ Dexamethasone 1mg qd + Zoledronate 4mgIV q4W vs zoledronate 4mgIV q4W					

AARPC= Androgen Ablation-refractory Prostate Cancer; AC= abdominal cramp; AC= abdominal distension; AP= abdominal pain; BO= bowel obstruction; CID= Chemotherapy-induced diarrhea; CT= d=days; GEP= gastroenteropancreatic; HCC= hepatocellular cancer; IM= intramuscular; KPS= Kaenofsky performance status; M=month(s); NET= neuroendocrine tumours; LA= long acting; mos=months; n= number enrolled; OIR= Overall improvement rate; OS= overall survival; PT=progression time; q= every; QoL= quality of life; RT= Radiation therapy; TR= tumor response; TTP=time to tumor progression; ST= Survival time; W= week(s); X= times; Yr= year(s);
*= primary outcome
** Non controlled trial.

Instructions. These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order, following the instructions in the black boxes as you go.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	1. Seems to; four negative trials counter recommendation #1 & 1 negative trial counters recommendation # 2; no new data for recommendation #4
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2. No
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	3. Not likely
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	4. I anticipate so

5. If Q2, Q3, and Q4 were all answered NO, this document should be **ARCHIVED** with no further action.

Review Outcome	ARCHIVE
DSG/GDG Approval Date	11 December 2012

DSG/GDG Commentary	None

New References Identified:

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Literature Search Strategy:

Medline

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. exp neoplasms/ or cancer/ or tumor/ or carcinoid/
32. (octreotide or sandostatin).tw.
33. 31 and 32
34. (200425$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 201223$).ew.
35. 33 and 34
36. limit 35 to (human and english language)

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
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12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
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ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: octreotide AND (diarrhea OR carcinoid OR neuroendocrine OR (bowel obstruction))

REVIEW OUTCOMES DEFINITIONS

1. **ARCHIVED –** An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. **ENDORSED –** An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY –** A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making**.**