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DQTC-SOS Advice Report 3 EDUCATION AND INFORMATION 2012

The Role of Porfimer Sodium (Photofrin™) in the Palliative Treatment of Esophageal Cancer

R.A. Malthaner and R.B. Rumble,
on behalf of Cancer Care Ontario's Program in Evidence-based Care

Report Date: January 11, 2006

This DQTC-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
The report, which consists of a Summary and a Full Report, is available on the CCO web site (http://www.cancercare.on.ca).

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The 2006 guideline recommendations were put in the

Education and Information section

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Education and Information

Report Date: January 11, 2006

SUMMARY

Question
What is the role of porfimer sodium in the palliative treatment of esophageal cancer? Outcomes of interest are relief from symptoms, including dysphagia and pain, and quality of life scores.

Target Population
These recommendations apply to adult patients with esophageal cancer for whom palliative treatment is the therapy of choice.

Recommendations
See Appendix 2 for the regimens and dosages used in the included trials.

The current standard of care for patients undergoing palliative therapy for esophageal cancer is best supportive care including the use of flexible metal stents inserted to restore esophageal patency.

For patients with contraindications to the insertion of flexible stents, photodynamic therapy with porfimer sodium is a palliative therapy option if the goal of treatment is relief from dysphagia; however, this recommendation is based on expert opinion, and is not based on evidence from a randomized comparison between photodynamic therapy with porfimer sodium and flexible metal stents.

Evidence

Currently, the only randomized comparisons available on the use of photodynamic therapy using porfimer sodium are with laser therapy, and laser therapy is rapidly falling out of favour with many clinicians because it is cumbersome, of questionable efficacy, and in many cases, it requires multiple treatments. Evidence reviewed in this report did not detect a statistically significant difference between photodynamic therapy with porfimer sodium compared with Nd:YAG laser for dysphagia palliation. While there may be a benefit for patients given porfimer sodium in dietary status at one month as was found in one of the trials (4), further trials are need to confirm this observation. This same trial also found a quality of life benefit for porfimer sodium compared with Nd:YAG laser, and treatment with Nd:YAG laser was associated with a drop from baseline quality of life scores.

Future Research

Currently, there are no randomized trials available comparing any photodynamic therapy option (porfimer sodium or other) to what many experts consider the best supportive standard of care, that being the insertion of flexible stents into the esophagus. Future trials should address this lack of data by performing a randomized trial comparing porfimer sodium, or another photodynamic therapy with suspected efficacy, against the latest generation of flexible stents.

Related PEBC documents

- Practice Guideline Report #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.
- Practice Guideline Report #2-12: *Combined Modality Radiotherapy and Chemotherapy in the Non-Surgical Management of Localized Carcinoma of the Esophagus*.

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FULL REPORT

I. QUESTION

What is the role of porfimer sodium in the palliative treatment of esophageal cancer? Outcomes of interest are relief from symptoms, including pain and dysphagia, and quality of life scores.

II. CHOICE OF TOPIC AND RATIONALE

Cancer of the esophagus appears in two main histological sub-types: squamous cell carcinoma arising in the epithelial tissue and adenocarcinoma arising in glandular tissue (1). In the past, squamous cell carcinoma was the most common sub-type, but today the incidence of adenocarcinoma is rising in North America and parts of Western Europe while the incidence rates of squamous cell carcinoma have remained relatively constant (1). In Canada, the projected 2005 incidence rates for esophageal cancer are 1,450 new cases (1,050 in males and 400 in females) (2). The projected mortality rates for esophageal cancer are approximately 1,600 deaths (an estimated 1,200 in males and 420 in females), equal to a deaths/case ratio of 1.13 for the total population (1.16 for males and 1.05 for females) (2). While many patients present with earlier, resectable disease, many other patients present with esophageal cancer that is not surgically resectable as the tumour is locally advanced, or has metastasized into other areas, and these patients require some form of palliative treatment to provide relief from dysphagia and pain (1). There are currently several options available for the palliation of symptoms from esophageal cancer including: external-beam radiation therapy, intraluminal brachytherapy, intubation through the tumour, stenting, laser treatment, and dilation (1); however, once these options have been exhausted, or if there are contraindications for their use, patients are left with no further treatment choices. For this reason, clinicians would be interested in any intervention in addition to the previously mentioned options that would help to improve the outcomes of palliative treatment in this population. Photodynamic therapy with porfimer sodium may be a suitable candidate for this.

Photodynamic therapy (PDT) is possible because of the differential accumulation of photosensitizing agents in dysplastic or malignant tissue (3). After administration, the photosensitizer drug predominantly accumulates in tumour tissue and remains available until light activation (3), which takes place 40-50 hours later. Three elements are required for a PDT reaction to occur: the photosensitizing agent, light, and oxygen (3). When light is applied directly to the sensitized tissue, the photodynamic reaction induces photochemical destruction of the tumour cells by several mechanisms including: singlet oxygen release, direct mucosal damage leading to cell necrosis, apoptosis, or ischemia combined with vascular shutdown and also inflammatory immune responses (3). Any PDT effect will vary according to the type of photosensitizer used, the wavelength and intensity of the light source used, and the type of light distribution system (3).

Most studies of PDT in gastroenterology performed to date have focused on hematoporphyrin derivative or its derivative porfimer sodium (marketed as Photofrin™ by Axcan Pharma Inc.) (3). Other PDT agents available include meta-tetrahydroxyphenal chlorine, 5-aminolevulinic acid, and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a, but evidence on these agents is lacking (3).

Considering the interest by some Ontario clinicians to have access to this new treatment, the Drug Quality Therapeutic Committee's Standing Oncology Subcommittee (DQTC-SOS) approached Cancer Care Ontario's Program in Evidence-based Care (PEBC) to provide advice, informed by the clinical evidence, as to the role of porfimer sodium in the palliative treatment of esophageal cancer. This advice report, developed by the PEBC with input from the Gastrointestinal Disease Site Group (DSG), provides a

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systematic review of the available evidence, data synthesis, clinical interpretation, and recommendations that will be used by the DQTC–SOS to make funding and policy recommendations.

III. METHODS

This advice report was commissioned by the Program in Evidence-based Care. A member of the Gastrointestinal Cancer DSG (Dr. Malthaner) agreed to serve as the clinical lead on this topic as it was not formally part of the Gastrointestinal Cancer DSG's portfolio. This advice report is a convenient and up-to-date source of the best available evidence on the role of porfimer sodium in the palliative treatment of esophageal cancer, developed through a systematic review of the available evidence. The authors disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

Literature Search Strategy

The MEDLINE (1966 through November (week 3) 2005), CANCERLIT (1975 through July 2002), and the Cochrane Library (through Issue 3, 2005) databases were searched for relevant information using the following terms. The term "esophageal neoplasm" (Medical subject heading (MeSH)) was combined with "phototherapy" (MeSH), "photochemotherapy" (MeSH), "photodynamic therapy (MeSH), "hematoporphyrin" (MeSH), and "dihematoporphyrin" (MeSH). These MeSH terms were then combined with following text words, "esophageal cancer", esophageal carcinoma", "esophageal cancer", "esophageal carcinoma", "photofrin", "porfirmer sodium", "porphyrin", "esophageal malignancy", and "esophageal malignancy". Search terms describing study designs were not used.

Abstracts published in the 2000-2005 proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO), including abstracts from the Gastrointestinal Cancer Symposiums, were systematically searched for evidence relevant to this advice document. Additionally, the U.S. National Guidelines Clearinghouse (NGC) (http://www.guideline.gov/index.asp), the Canadian Medical Association (CMA) InfoBase of clinical practice guidelines (http://mdm.ca/cpgsnew/cpgs/index.asp), and the National Cancer Institute's (NCI®) database of clinical trials (http://www.nci.nih.gov/search/clinical trials/) were searched for relevant information (see Appendix 1 for search terms used). Search terms used for the ASCO abstracts, NGC database, and the CMA InfoBase included "photodynamic", "PDT", "esophagus", "esophageal", and "photofrin". Search terms used in the NCI® search included "esophageal cancer", "treatment", "phototherapy", "phase II" and "phase III".

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports of:

1. Randomized controlled trials (RCTs) comparing porfimer sodium with any other therapy in the palliative treatment of esophageal cancer.
2. Phase II trials comparing porfimer sodium with any other therapy in the palliative treatment of esophageal cancer.

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Exclusion Criteria

1. Studies published in languages other than English.
2. Studies enrolling less than 10 patients.
3. Studies examining the use of PDT in Barrett's esophagus.
4. Letters and editorials.
5. Non-human studies.

Synthesizing the Evidence

As only two RCTs were obtained, no pooling of outcome data was performed.

IV. RESULTS

Literature Search Results

A total of three reports met the inclusion criteria and were obtained (4,5,6). Two of these trials were RCTs (4,5) and one was a Phase II trial (6). The sample sizes of the trials obtained ranged from a low of 20 patients (6) to a high of 236 patients (5). Both of the RCTs compared photodynamic therapy using photofrin with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy. Both of the RCTs (4,5) reported partial funding from a pharmaceutical company (4; Johnson & Johnson; American Cyanamid) (5; Quadra Logic Technologies; American Cyanamid). The phase II trial (6) did not report the source of funding.

Outcomes

See Appendix 2 for dosages used in the trials reviewed.

Dysphagia Score Outcomes

All three trials (4,5,6) provided data on the change in dysphagia scores. Of the RCTs, the trial by Heier et al (4) reported no difference in outcome between PDT with porfimer sodium and Nd:YAG laser in the relief of dysphagia. However, it was noted in this trial that when one month results were compared with baseline values treatment with porfimer sodium was associated with a greater increase in dietary performance (PDT +1.8±1.2 versus Nd:YAG +1.0±1.5; p=0.006) and esophageal grade (PDT +22.4±15.4 versus Nd:YAG +7.0±17.5; p=0.002). The trial by Lightdale et al (5) reported dysphagia outcomes at baseline, week one, and month one for both PDT and Nd:YAG, with results being that both treatments achieved a significant mean improvement over baseline numbers of ¾ of a grade at both week one and month one. Of the responders (defined as an improvement of at least one grade) half had a response of two or more grades or achieved normal swallowing. In both the PDT and the Nd:YAG groups, about 25% of all patients showed no change in dysphagia scores during the trial.

The phase II trial reported that the dysphagia scores improved in grade from a mean of 4.0 to 2.8 as measured by the Krasmer scale (see Appendix 3 for an example of a generic dysphagia scale).

Quality of Life

Only one of the studies reviewed provided data on quality of life (4), which detected a statistically significant improvement ($p<0.001$) in baseline quality of life scores for treatment with porfimer sodium compared with treatment with Nd:YAG laser as measured by the Karnofsky performance status scale (a scale that measures both symptoms and levels of independent activity). Treatment with Nd:YAG laser was associated with a drop in quality of life scores.

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Pain Score Outcomes

None of the studies reviewed reported on pain scores.

Table 1. Treatment outcomes by study.

Study	Inclusion criteria	Interventions	N	Dysphagia	Quality of life
Heier SK et al, 1995 [USA] (4)	Patients with dysphagia caused by biopsy-proven esophageal cancer that were not suitable for, or had refused, surgery, RT, or CT. At least one month must have passed after any prior treatment before enrollment.	PDT	22	None: 12 pts Solids: 7 pts Soft solids: 1 pts Liquids: 0 pts Saliva: 0 pts	+7.2±14.5
		Nd:YAG	20	None: 11 pts Solids: 4 pts Soft solids: 3 pts Liquids: 0 pts Saliva: 0 pts p=0.6 (n.s.)	-7.2±14.3 p<0.001
Lightdale CJ et al, 1995 [USA] (5)	Patients with biopsy-verified esophageal cancer that were not suitable for, or had refused, failed to respond to, or had a recurrence following surgery, CT, or RT. Additional entry requirements were patients must be symptomatic, have dysphagia to solid foods due to the disease, and a Karnofsky performance status of at least 30%.	PDT	110	-0.75	NR
		Nd:YAG	108	-0.68 Average change from baseline scores at end of month one. p>0.05 (n.s.)	
Okunaka T et al, 1990 [Japan/USA] (6)	Patients with esophageal cancer categorized as having either early-stage superficial lesions or advanced invasive lesions.	PDT	20	Improved from grade 4.0 to grade 2.8	NR

Note: N, number; PDT, photodynamic therapy; Nd:YAG, neodymium:yttrium-aluminum-garnet laser; RT, radiotherapy; CT, chemotherapy; NR, not reported; n.s., not significant.

Adverse Effects

Both of the RCTs (4,5) provided data on adverse effects. The Phase II trial reported no adverse event rates. In the RCTs, photodynamic therapy was associated with the following adverse effects: skin photoreactions (4,5), fistula (4), fever (4,5), luminal plugging (4), nausea (5), pleural effusion (5), and esophageal perforation (5). Table 2 details the adverse effects observed in the two RCTs. No grades were given for any of the reported adverse effects.

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Table 2. Adverse effects by study.

Study	Intervention [N]	Skin photo-reactions %	Fistula %	Fever %	Luminal plugging %	Nausea %	Pleural effusion %	Esophageal perforation %
Heier SK et al, 1995 [USA] (4)	PDT [22]	18	4.5	22.7	22.7	NR	NR	NR
	Nd:YAG [20]	0	10	5	25	NR	NR	NR
Lightdale CJ et al, 1995 [USA] (5)	PDT [110]	19	NR	16	NR	8	10	1
	Nd:YAG [108]	0	NR	5	NR	2	2	7

Note: PDT, photodynamic therapy; Nd:YAG, neodymium:yttrium-aluminum-garnet laser; NR, not reported.

V. INTERPRETIVE SUMMARY

The evidence reviewed did not detect a statistically significant difference between photodynamic therapy with porfimer sodium compared with Nd:YAG laser for dysphagia palliation ($p>0.05$). There may be a benefit for patients given porfimer sodium in dietary status at one month as was found in one of the trials (4), but further trials are need to confirm this observation. This same trial also found a quality of life benefit for porfimer sodium compared with Nd:YAG laser, and treatment with Nd:YAG laser was associated with a drop from baseline quality of life scores.

While randomized trials are available comparing photodynamic therapy using porfimer sodium to Nd:YAG laser, many experts do not feel that Nd:YAG is the appropriate comparator anymore, and are instead advocating best supportive care and the insertion of flexible metal stents to palliate the effects of dysphagia and restore esophageal patency (7,8). Following insertion of a current generation flexible metal stent, most patients experience rapid improvement of dysphagia with median scores improving from grade 3 (able to drink liquids only) to a median of grade 1 (able to eat most solid foods) (8). While these stents are effective for palliating the effects of obstructive esophageal cancer, they also have some disadvantages including pain, severe gastrointestinal reflux, stent migration, and the possibility of tumour in-growth into the stent itself (7). As detailed earlier in this report, therapy with porfimer sodium also carries some risks, some of which are potentially life-threatening (e.g. esophageal perforation). Unfortunately, no published randomized trials are available comparing photodynamic therapy with porfimer sodium to the latest generation of flexible metal stents.

In consideration of the lack of comparative evidence on what the authors believe to be the existing standard of care (best supportive care and the insertion of flexible metal stents) with photodynamic therapy using porfimer sodium, we recommend the following: for patients with contraindications to the insertion of flexible stents, photodynamic therapy with porfimer sodium is a palliative therapy option if the goal of treatment is relief from dysphagia; however, the authors acknowledge that this recommendation is based on expert opinion, and is not based on evidence from a randomized comparison between photodynamic therapy with porfimer sodium and flexible metal stents.

VI. RECOMMENDATIONS AND EVIDENCE

Recommendations

See Appendix 2 for the regimens and dosages used in the included trials.

Education and Information

The current standard of care for patients undergoing palliative therapy for esophageal cancer is best supportive care including the use of flexible metal stents inserted to restore esophageal patency.

For patients with contraindications to the insertion of flexible stents, photodynamic therapy with porfimer sodium is a palliative therapy option if the goal of treatment is relief from dysphagia; however, this recommendation is based on expert opinion, and is not based on evidence from a randomized comparison between photodynamic therapy with porfimer sodium and flexible metal stents.

Evidence

Currently, the only randomized comparisons available on the use of photodynamic therapy using porfimer sodium are with laser therapy, and laser therapy is rapidly falling out of favour with many clinicians because it is cumbersome, of questionable efficacy, and in many cases, it requires multiple treatments. Evidence reviewed in this report did not detect a statistically significant difference between photodynamic therapy with porfimer sodium compared with Nd:YAG laser for dysphagia palliation. While there may be a benefit for patients given porfimer sodium in dietary status at one month as was found in one of the trials (4), further trials are need to confirm this observation. This same trial also found a quality of life benefit for porfimer sodium compared with Nd:YAG laser, and treatment with Nd:YAG laser was associated with a drop from baseline quality of life scores.

Future Research

Currently, there are no randomized trials available comparing any photodynamic therapy option (porfimer sodium or other) to what many experts consider the best supportive standard of care, that being the insertion of flexible stents into the esophagus. Future trials should address this lack of data by performing a randomized trial comparing porfimer sodium, or another photodynamic therapy with suspected efficacy, against the latest generation of flexible stents.

Related PEBC Guidelines

- Practice Guideline Report #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.
- Practice Guideline Report #2-12: *Combined Modality Radiotherapy and Chemotherapy in the Non-Surgical Management of Localized Carcinoma of the Esophagus*.

VII. CONFLICTS OF INTEREST

Neither of the authors declared any conflicts of interest.

VIII. ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. R. Malthaner and Mr. R.B. Rumble for taking the lead in drafting and revising this DQTC-SOS advice report.

For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca/.

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Appendix 1. Ongoing trials.

A search of the National Cancer Institute's (NCI®) database of ongoing clinical trials on December 13, 2005 did not locate any relevant trials.
(http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx)

Type of cancer:	Esophageal
Type of trial:	Treatment; stage III/IV
Status:	Active
Type of intervention:	Photodynamic therapy
Drug:	Photofrin, photofrin II
Phase of trial:	Phase II, phase III

Appendix 2. Dosing by trial.

Heir SK et al, 1995 (4)
PDT: 2 mg/kg of body weight IV followed by argon pumped dye laser tuned to 630±2 nm red light administered by cylinder-diffusing fibres, with lengths varying from 1.0 to 2.5 cm, at a rate of 400 mW/cm. Limited to two applications. **Nd:YAG:** Standard technique at a set power level of 90 W. Administered every 2 to 4 days until luminal patency was restored.
Lightdale CJ et al, 1995 (5)
PDT: 2 mg/kg of body weight IV followed by argon pumped dye laser tuned to 630 nm red light administered by cylinder-diffusing fibres, with lengths varying up to 2.5 cm, at a rate of 400 mW/cm. Limited to three applications at one-month intervals. **Nd:YAG:** Standard technique at a set power level ranging from 15 to 90 W and with a pulse duration of 0.5 to 4.0 seconds. Administered until dysphagia had been successfully palliated or until the investigator believed further treatment would be futile.
Okunaka T, 1990 (6)
Patients received either: 3 mg/kg HpD (Photofrin) or 2 mg/kg porfimer sodium (Photofrin II) IV followed by argon pumped dye laser tuned to 630 nm red light administered by cylinder-diffusing fibres, with lengths varying from 1 to 3 cm, at a rate of 400 mW/cm.

Appendix 3. Generic Dysphagia Scale

Grade 1:	Normal swallowing
Grade 2:	Difficulty swallowing some hard solids; can swallow semisolids
Grade 3:	Unable to swallow any solids; can swallow liquids
Grade 4:	Difficulty swallowing liquids
Grade 5:	Unable to swallow saliva

Note: This generic dysphagia scale was taken from: http://www.rxlist.com/cgi/generic3/photofrin_cp.htm [accessed January 11, 2006].

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