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## The Role of Amifostine as a Radioprotectant in the Management of Patients with Squamous Cell Head and Neck Cancer Practice Guideline Report # 5-8

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ORIGINAL GUIDELINE: May 13, 2003

NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: November 18 2003

MOST RECENT LITERATURE SEARCH: March 2004

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

### SUMMARY

#### Guideline Question

For patients with squamous cell head and neck cancer, does amifostine safely and effectively ameliorate important side effects of radiotherapy with acceptable toxicity and no tumour protection? Xerostomia, mucositis, and the anti-tumour effects of amifostine were the main outcomes of interest.

#### Target Population

These recommendations apply to adult patients with any stage of squamous cell head and neck cancer who are receiving radical radiotherapy, encompassing at least 75% of the parotid glands, with or without concurrent chemotherapy.

#### Recommendations

- On the basis of the available data, amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin.
- The recommended dose and administration of amifostine is an intravenous infusion 15 to 30 minutes prior to radiation, with standard doses of 500mg or doses ranging from 200mg/m<sup>2</sup> to 300 mg/m<sup>2</sup>. The Head and Neck Cancer Disease Site Group would be supportive of randomized trials designed to compare amifostine delivered subcutaneously versus intravenously.
- Data on the protective effect of amifostine from mucositis are inconclusive at this time.

## **Qualifying Statements**

- For suitable patients with stage III/IV squamous cell carcinoma, a common practice in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.
- The data on tumour control and survival outcomes support the conclusion that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available for this population of patients.
- Nausea, vomiting, hypotension, and allergic reactions were reported as the most common side effects of amifostine, but they were rarely severe ( $\geq$  grade 3).

## **Methods**

The literature was searched using MEDLINE (1966 through January 2003), CANCELIT (1983 through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, and abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1998-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002), and the European Society for Medical Oncology (1998, 2000). Reference lists from relevant articles and reviews were searched for additional trials.

Evidence was selected and reviewed by members of the Practice Guidelines Initiative's Head and Neck Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Head and Neck Cancer Disease Site Group, which comprises surgeons, medical oncologists, and radiation oncologists.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report was 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 process consists of the periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline.

## **Update**

The original literature search has been updated using MEDLINE (January 2003 through March 2004), EMBASE (1980 through March 2004), the Cochrane Library (Issue 1, 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 (2003), the American Society for Therapeutic Radiology and Oncology (2003), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to march 2004 for evidence relevant to this practice guideline report. Please note that CANCELIT is no longer included in update searches: results from an internal PGI project indicated that the overlap with MEDLINE is 100%, making CANCELIT database searches redundant.

## **Key Evidence**

- Six randomized trials (five published and one presented as an abstract), one quality-of-life paper, and one practice guideline were eligible for inclusion in the systematic review of the evidence.

- The only large randomized trial detected a significant reduction in the severity of acute and chronic xerostomia but not mucositis, with amifostine added to radiotherapy for head and neck cancer.
- From the available data, pooled results across trials indicate that patients had significantly less acute and late xerostomia with amifostine added to radiotherapy or radiochemotherapy with standard-dose carboplatin for head and neck cancer. There were no statistically significant differences in mucositis. Data from one randomized trial have yet to be presented.
- Results indicate that amifostine does not affect the anti-tumour effectiveness of radiotherapy with or without concurrent chemotherapy with carboplatin.
- Nausea, vomiting, hypotension, and allergic reactions were the most commonly reported side effects of amifostine, but they were rarely severe ( $\geq$  grade 3).

### Update

- One small randomized trial comparing amifostine to control and one randomized trial comparing subcutaneous with intravenous amifostine administration were identified and included in the systematic review of the evidence.
- The second bullet has been revised through the editorial process to provide greater clarity and should now read:
 

Of the seven randomized trials comparing amifostine to control or placebo, only one trial randomized more than 100 patients per treatment arm. That trial detected a significant reduction in the severity of acute and chronic xerostomia, but not mucositis, with amifostine added to radiotherapy for head and neck cancer.
- The last sentence of the third bullet has been revised through the editorial process to provide greater clarity and should now read:
 

Data from one randomized trial published as an abstract have yet to be presented.

### Future Research

Randomized trials of amifostine are needed to address issues of efficacy related to concomitant low-dose daily cisplatin or carboplatin, tumour protection, minimally effective doses, optimal routes of delivery, quality of life, and total healthcare costs.

### Related Guidelines

Practice Guidelines Initiative's Practice Guideline Reports:

- #12-6: *Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer.*
- #5-5: *Symptomatic treatment of radiation induced xerostomia in head and neck cancer patients.*

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## **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.<sup>1</sup> 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 (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario 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:

<sup>1</sup> 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 the CCO Internet site at:  
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