Radiopharmaceuticals for the Palliation of Painful Bone Metastases

Report Date: June 15, 2004

An assessment was conducted in November 2012 placed Practice Guideline Report 14-1 IN REVIEW. This means that it is undergoing a review for currency and relevance. The PEBC has determined that it is still appropriate for this document to continue to be available while this updating process unfolds.

Practice Guideline (PG) 14-1, consists of two sections:
- Section 1: Summary
- Section 2: Full Report

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Radiation Therapy Program web page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/radther/

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

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Radiopharmaceuticals for the Palliation of Painful Bone Metastases
Practice Guideline Report #14-1

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SUMMARY

Guideline Question
What is the role of radiopharmaceuticals in the palliation of metastatic bone pain? Outcomes of interest are pain response, analgesic consumption, overall survival, adverse effects and quality of life.

Target Population
These recommendations apply to adult cancer patients with uncomplicated, multifocal painful bone metastases above and below the diaphragm whose pain is not controlled with conventional analgesic regimens and where increased uptake in the painful lesions is demonstrated on bone scan.

Recommendations
- Use of radiopharmaceuticals (strontium-89 and samarium-153) may be considered as an option for the palliation of multiple sites of bone pain from metastatic prostate cancer as these patients represented the majority (80%) of patients experiencing benefit in clinical trials where histology was specified.
- Use of radiopharmaceuticals (strontium-89 and samarium-153) may also be considered for patients with lung and breast cancers. These patients represented a substantial minority (20%) in the clinical trials where histology was specified.
- The selection of patients for radiopharmaceutical therapy should consider the patient’s marrow function, performance status, recent use of other marrow suppression agents (chemotherapy or radiotherapy), unsuitability for alternate palliative interventions (wide field or local field radiotherapy, hormone therapy, chemotherapy, bisphosphonates) and anticipated life expectancy.
- Ideally the decision for radiopharmaceutical use should be based on a multidisciplinary (radiation oncology, nuclear medicine, medical oncology, palliative care) patient assessment.
- Patients with a partial response or complete response following radiopharmaceutical therapy may be considered for repeat administration for persistent or recurrent bone pain if the following is ruled out: rapid systemic disease progression, mechanical component to bone pain, underlying other bone pathology, impending or established fracture or spinal cord compression.
- The recommended dose for strontium-89 is 148 mBq (4mCi) by slow intravenous injection (1-2 minutes), accompanied by intravenous or oral hydration (at least 500 mL). The recommended dose for samarium-153 is 37 mBq/kg (1 mCi/kg) by slow intravenous injection (1-2 minutes), accompanied by intravenous or oral hydration (at least 500 mL).
Qualifying Statements

- Patients with painful bone metastases should have appropriate analgesic and supportive care measures instituted in addition to other palliative interventions such as radiopharmaceuticals.
- Patients with more limited painful bone involvement, or painful lesions confined to one side of the diaphragm should be considered for focal or wide field (hemibody) external beam radiotherapy. Information on histologic subtype was not available for a significant proportion (30-40%) of patients treated on trials of palliative radiopharmaceuticals.
- The cost benefit of single-agent radiopharmaceuticals relative to other systemic agents such as bisphosphonates and chemotherapy remains to be determined.
- A subset of trials has suggested an increased benefit in terms of pain palliation with the combination of a radiopharmaceutical agent with external beam radiotherapy or chemotherapy. The combination of radiopharmaceuticals with these modalities or with others such as bisphosphonates requires further investigation in clinical trials.
- The administration of radiopharmaceuticals should be restricted to those patients with adequate bone marrow reserve and performance status (Karnofsky Performance Status >60), anticipated life expectancy of greater than four months and uncomplicated bone metastases (no pathologic fracture or impending pathologic fracture, no spinal cord compression or no hypercalcemia).
- The use of newer radiopharmaceuticals such as rhenium and radioactive tin are under investigation for the palliation of metastatic bone pain but are not approved for use outside clinical trials in Canada.
- Samarium-153 is currently licensed in Canada, but there is no distributor at this time.

Methods

Entries to MEDLINE (1966 through January 2004), EMBASE (1980 to 2004 week 10), CANCERLIT (1975 through October 2002) and Cochrane Library (2003, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the Society of Nuclear Medicine, the American Society of Clinical Oncology, the European Association of Nuclear Medicine and the American Society for Therapeutic Radiology and Oncology were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative’s Therapeutic Radiopharmaceutical Guidelines Group and methodologists. This practice guideline report has been reviewed and approved by the Therapeutic Radiopharmaceutical Guidelines Group, which comprises medical oncologists, radiation oncologists, an endocrinologist and physicians specializing in nuclear medicine. There are currently no patient representatives on the Therapeutic Radiopharmaceutical Guidelines Group.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the guideline report is 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 information.

Key Evidence

**Strontium-89**

- Six randomized phase III trials, one randomized phase II trial and one randomized crossover trial of strontium-89 were reviewed and form the basis of the evidence for this radiopharmaceutical. Twenty-seven additional phase II trials, phase I trials, and
retrospective case series were reviewed to provide evidence for the effect on different primary tumour sites.

- A randomized phase III trial comparing strontium-89 plus cisplatin with strontium-89 plus placebo reported a significantly higher proportion of patients experiencing pain relief for a significantly longer duration with strontium-89 plus cisplatin.
- In a randomized phase III trial comparing adjuvant strontium-89 with placebo following radiotherapy, a higher proportion of patients were pain-free with strontium-89. Patients who received strontium-89 also experienced fewer new sites of bone pain. A second, but underpowered, study failed to confirm those results.
- In one randomized trial of strontium-89 versus local radiotherapy, median overall survival was improved with radiotherapy. Pain response and time-to-progression were similar in the two groups. In a second randomized trial of strontium-89 versus radiotherapy (hemibody or local), patients treated with strontium-89 developed fewer new sites of pain.
- One randomized phase III trial reported no difference in pain relief between strontium-89 and placebo.

**Samarium-153**

- Three randomized phase III trials (two full papers and one abstract) and two randomized phase II trials form the basis of the evidence for this radiopharmaceutical. Six additional phase II trials and phase I trials were reviewed to provide additional evidence.
- In a randomized phase III trial of three different doses of samarium-153, the pain responses were similar for all three doses.
- In a randomized phase III trial of two different doses of samarium-153 versus placebo, the complete pain response rate was significantly higher with the higher dose of samarium-153 compared with placebo.
- In a randomized phase III trial comparing samarium-153 with placebo, significant differences favouring samarium-153 were reported for pain and opiate use.

**Additional Radiopharmaceuticals**

- One randomized phase III trial, two randomized phase II trials, one randomized crossover trial and 13 phase II or phase I trials of rhenium were located and reviewed. There is insufficient evidence to inform a recommendation for rhenium at this time.
- One phase I trial of tin-117m and one phase II trial of phosphorus-32 were located and reviewed. There is insufficient evidence to inform a recommendation for either of these two agents at this time.

**Treatment Alternatives**

- Patients with one or two sites of painful bone metastases may benefit from focal palliative external beam radiotherapy (see the Practice Guidelines Initiative’s Practice Guideline Report #13-2, *Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases*). Patients with multiple painful sites confined to one region of the body (i.e., upper body or lower body) may benefit from single fraction hemibody irradiation.
- Patients with multiple sites of painful bone metastases may benefit from other systemic interventions such as hormonal therapy, bisphosphonate therapy or palliative chemotherapy, depending on the cancer histology and clinical situation.

**Future Research**

Ongoing studies are required to evaluate newer radiopharmaceuticals (i.e., radioactive tin and rhenium), compare existing radiopharmaceuticals (i.e. strontium-89 versus samarium-153), determine the optimal dose and timing of radiopharmaceuticals, determine the efficacy of
re-treatment with radiopharmaceuticals and compare radiopharmaceuticals with other agents such as external beam radiotherapy and chemotherapy.

Related Guidelines
Practice Guidelines Initiative’s Practice Guideline Reports:
- #3-6: Use of Strontium-89 in Patients with Endocrine-refractory Carcinoma of the Prostate Metastatic to Bone.
- #13-2: Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases.

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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.\(^1\) 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 (PGCC), 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, which is expected to consult with relevant stakeholders, including CCO.

Reference:

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