



## Complete Summary

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### GUIDELINE TITLE

Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a clinical practice guideline.

### BIBLIOGRAPHIC SOURCE(S)

Hotte S, Waldron T, Canil C, Winquist E, Genitourinary Cancer Disease Site Group. Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 8. 27 p. (Evidence-based series; no. 3-8-2). [57 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Unresectable or metastatic renal cell cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Oncology  
Urology

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

To evaluate whether there is a role for interleukin-2 (IL-2) in the treatment of patients with unresectable or metastatic renal cell carcinoma (RCC), when compared to non-interleukin-2 containing regimens, for improving overall or progression-free survival, response rate, and quality of life considering its adverse effects

### **TARGET POPULATION**

Patients with unresectable or metastatic renal cell cancer

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Interleukin-2 (IL-2) containing regimens

Note: Non-high-dose IL-2-containing regimens are not recommended. High-dose IL-2 is recommended only in the context of a clinical trial or investigational setting.

### **MAJOR OUTCOMES CONSIDERED**

- Overall survival
- Progression-free survival
- Response rate
- Quality of life
- Adverse effects

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

## **Literature Search Strategy**

MEDLINE (1966 through February 2005), EMBASE (1980 through 2005 week 9), and CANCERLIT (1975 through October 2002) databases were searched for relevant papers. MEDLINE was searched using the following medical subject headings: "Carcinoma, renal cell," "kidney neoplasms," "immunotherapy," "interleukin-2," and "interleukin;" EMBASE was searched using the following Excerpta Medica tree terms: "kidney tumor," "kidney cancer," "immunotherapy," and "interleukin 2." In each database, those subject headings were combined with the following disease and treatment-specific text words: "renal cancer," "kidney cancer," "immunotherapy:" "interleukin," and "IL-2." Those terms were then combined with search terms for the following publication types and study designs: randomized controlled trials, controlled clinical trials, meta-analyses, systematic reviews, and practice guidelines.

In addition, the Cochrane Library databases (2004, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (1995-2005) and the American Urological Association (1995-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by four reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

## **Study Selection Criteria**

Articles were selected for inclusion in this systematic review if they were fully published reports or abstracts of randomized controlled trials (RCTs) or meta-analyses of randomized controlled trials comparing interleukin-2 (IL-2)-containing treatment regimens to regimens without interleukin-2 in patients with unresectable or metastatic renal cell carcinoma (RCC). Reports were required to provide data on at least one of the following outcomes: survival (i.e., overall, progression-free, or time-to-progression), response rate, toxicity, or quality of life. Reports including non-renal cell carcinoma patients were eligible as long as the outcomes for renal cell carcinoma patients were analyzed separately. Existing systematic reviews or evidence-based practice guidelines relevant to the guideline question were also eligible. Randomized controlled trials that compared either surgery or radiotherapy with interleukin-2 immunotherapy were excluded.

## **NUMBER OF SOURCE DOCUMENTS**

Six randomized controlled trials and one systematic review with meta-analysis were reviewed.

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

### **Objective Response Rate**

To estimate the overall effect of interleukin-2 (IL-2)-based immunotherapy on response rate compared with non-IL-2 regimens, the response rates from individual randomized controlled trials (RCTs) were pooled and weighted according to the size of the treatment arms using the following formula:

$$pw = \text{sum}(w_i * p_i) / \text{sum}(w_i)$$

where:

$pw$  = the weighted mean of  $i$  studies

$p_i$  = response rate expressed as a proportion for study  $i$

$w_i$  = the weight for study  $i$

$v_i$  = the variance of the estimated proportion in study  $i$

In instances of a three-arm trial, where a treatment arm within a trial was used more than once to make comparisons (e.g., A versus [vs.] treatment B or A vs. treatment C), the weighted objective response rate for the treatment arm only contributed once to the analysis.

### **Mortality at One Year**

Survival data were available for all six randomized controlled trials included in this review, either reported in the text or extractable from survival curves. To estimate the overall effect of IL-2-based immunotherapy on mortality, data were pooled at a common time point (e.g., mortality at one year). The time point selected for the meta-analysis must be clinically credible and relevant but not so far along the survival curve that wide confidence intervals result from fewer patients contributing to the pooled estimate. Since time points prior to the median will generally ensure that there is sufficient data to be credible, a pooled median survival time (weighted by the size of the treatment arms) was calculated to determine an appropriate time point for pooling. The meta-analysis was performed using one-year mortality data because the pooled weighted median survival times were 19.4 months and 10.8 months for IL-2-containing arms and non-IL-2 arms, respectively. For three-arm trials, mortality data from each IL-2-

containing arm were combined and then entered into the meta-analysis so that each arm only contributed once to the meta-analysis.

The meta-analysis was performed using Review Manager 4.2, available through the Cochrane Collaboration. The random effects model was used as the more conservative estimate of treatment effect. Results are expressed as relative risks (RR) with 95% confidence intervals (CI). An RR less than 1.0 favours the experimental arm (i.e., IL-2-based immunotherapy) and an RR greater than 1.0 favours the control arm. The meta-analysis results were examined for statistical heterogeneity by visual inspection of the forest plot and by calculating the Cochran Q (using a planned cut-off for significance of  $p < 0.05$ ) and I<sup>2</sup> (values of 25%, 50%, and 75% indicate low, moderate, and high degrees of heterogeneity) statistics.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

This evidence-based series was developed by the Genitourinary Cancer Disease Site Group (GU DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on interleukin-2 (IL-2) for unresectable or metastatic renal cell carcinoma (RCC), developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The GU DSG is comprised of medical and radiation oncologists, urologists, a pathologist, and methodologists.

Despite many years of research, the prognosis for patients with metastatic RCC remains poor, and no very effective treatment currently exists. Patients should therefore be encouraged to enter clinical trials whenever possible.

See the original guideline document for a discussion of the evidence used to formulate the recommendations.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

## Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included the following:

- *A request to add historical information on the evolution of agents for this disease, and a discussion of the current standard of care in Ontario.* The Genitourinary Cancer Disease Site Group (GU DSG) added additional historical information to the introduction of the report to provide context around the difficulties in assessing the clinical benefits associated with interleukin-2 (IL-2) and to discuss the issue of standard of care.
- *In discussing the two trials that showed a statistically significant but modest survival benefit, it was suggested the GU DSG discuss additional plausible explanations for the differences observed.* The GU DSG added more information on these two trials in order to provide further insight as to why the GU DSG believes the results of the trials need to be replicated in further studies before the regimens examined in these trials be considered standard treatment in metastatic renal cell carcinoma (RCC).
- *Minor editorial changes.* The GU DSG made suggested editorial changes.

## External Review

Feedback was obtained through a mailed survey of 92 practitioners in Ontario (medical oncologists and urologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on April 17, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- Non-high-dose interleukin-2 (IL-2)-containing regimens should not be used as standard treatment for unresectable or metastatic renal cell carcinoma (RCC).
- High-dose interleukin-2 should only be used by experienced physicians in the context of a clinical trial or investigational setting.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and a systematic review with meta-analysis.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Among the five trials reporting on objective response (eight comparisons), only three provided statistical comparisons of those data. Two trials (three comparisons) detected higher response rates with interleukin-2 (IL-2)-based therapy compared with non-IL-2 controls that were statistically significant. Combining the objective response rates from the five trials gave an overall weighted objective response rate of 13.3% (range, 9-39%) and 5.3% (0-20%) for IL-2-containing regimens and non-IL-2 regimens, respectively.
- Among the six trials reporting on survival, median survival data and one-year mortality data were available (reported or extracted from survival curves) from each trial report. Five of six trials provided statistical comparisons of median survival times between trial arms; two reported statistically significant longer survival with IL-2-based regimens over non-IL-2 controls and the remaining three trials reported no difference between arms. When the one-year mortality data were pooled in a meta-analysis, no statistically significant difference was observed between IL-2-based regimens versus non-IL-2 controls (relative risk [RR]=0.94; 95% confidence interval [CI], 0.67-1.30; p=0.69). A sensitivity analysis performed of two immunochemotherapy trials (IL-2-based regimens containing either 5-fluorouracil or fluorouracil) detected a statistically significant reduction in one-year mortality with immunochemotherapy (relative risk=0.56; 95% confidence interval, 0.38-0.82; p=0.003); however, those trials have some methodological limitations.

### POTENTIAL HARMS

Toxicity data were described in all six trials. Interleukin-2 (IL-2)-based regimens were generally more toxic than non-interleukin-2 control regimens, but were described as moderately to well tolerated by most patients in the majority of trials. The majority of toxicities were graded as 1 or 2, but grade 3 or 4 toxicities were observed in a substantial number of patients. Fever (range, 2 to 56%), chills (3 to 6%), malaise (3 to 18%), anorexia (11 to 22%), oliguria (6 to 19%), nausea and/or vomiting (6 to 34%), diarrhea (1 to 28%), skin rash or allergies (3 to 11%), hypotension (6 to 68%), pulmonary distress (3 to 16%), and central nervous system (<2 to 14%) and cardiac toxicity (11 to 25%) were the most frequently reported grade 3/4 toxicities. No toxic deaths were reported in the two trials reporting those data.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Patients with unresectable or metastatic renal cell carcinoma (RCC) should be encouraged to participate in clinical trials.
- The Genitourinary Cancer Disease Site Group is currently reviewing evidence and developing guidelines on the use of interferon-alpha, and interferon-alpha combined with cytoreductive nephrectomy in patients with unresectable or metastatic renal cell carcinoma. These approaches show modest survival benefits in randomized trials and may be considered treatment options in this patient population.
- High-dose interleukin-2 (IL-2) has not been compared to appropriate comparators using non-interleukin-2-containing regimens in randomized trials, and so its effectiveness is unclear. Despite this, high-dose interleukin-2 is being used as a standard treatment for unresectable or metastatic renal cell carcinoma in much of the United States and parts of Europe based on single-arm studies.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Hotte S, Waldron T, Canil C, Winquist E, Genitourinary Cancer Disease Site Group. Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 8. 27 p. (Evidence-based series; no. 3-8-2). [57 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

**DATE RELEASED**

2006 Jun 8

**GUIDELINE DEVELOPER(S)**

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

**GUIDELINE DEVELOPER COMMENT**

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

**SOURCE(S) OF FUNDING**

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

**GUIDELINE COMMITTEE**

Provincial Genitourinary Cancer Disease Site Group

**COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

**FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

The members of the Genitourinary Cancer Disease Site Group (GU DSG) disclosed potential conflicts of interest relating to this systematic review and none were declared.

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**GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jun 8. Various p. (Practice guideline; no. 3-8-2). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- 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.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on October 26, 2006. The information was verified by the guideline developer on November 24, 2006.

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