



Evidence-based Series 3-8-2 Version 2- EDUCATION AND INFORMATION 2013

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

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer

Members of the Genitourinary Cancer Disease Site Group

An assessment conducted in November 2013 put Evidence-based Series 3-8-2 Version 2 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. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#)).

Evidence-based Series (EBS) 3-8-2 Version 2, the resulting review report, consists of the following 5 parts:

1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline
3. Section 2: Systematic Review
4. Section 3: Guideline Development and External Review
5. Document Assessment and Review Tool

and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Genitourinary Cancer Disease Site Group page at:
<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/>.

Release Date: September 15, 2011

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Evidence-based Series 3-8-2 Version 2

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Jun 2006	1966 to 2005	Full Report	Peer review publication ¹ Web publication	Not Applicable
Version 2 Sep 2011	2005 to 2010	New data found in Document and Assessment Review Tool	Updated Web publication	Evidence supports original recommendations. 2006 recommendations ENDORSED .

¹ Hotte S, Waldron T, Canil C, Winquist E. Interleukin-2 in the treatment of unresectable or metastatic renal cell cancer: a systematic review and practice guideline. Can Urol Assoc J. 2007;1(1):27-38.



Evidence-based Series 3-8-2 Version 2

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer

Guideline Review Summary

Review Date: March 2, 2011

The 2006 guideline recommendations are

ENDORSED

*This means that the recommendations are still current and
relevant for decision making.*

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2006. In March 2011, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Clinical Practice Guideline and Systematic Review in this version are the same as in the June 2006 version.

Update Strategy

The PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

Is there a role for single-agent high-dose interleukin-2 (IL-2) in the treatment of patients with unresectable or metastatic renal cell carcinoma (RCC) for improving overall or progression-free survival, response rate, and quality of life considering its adverse effects?

Literature Search and New Evidence

The new search (2005 to 2010) yielded three new studies evaluating single-agent high-dose IL2 in metastatic or unresected renal cell carcinoma, of which one was a full text

publication and two were abstracts. Brief results of these publications are shown in the [Document and Assessment Review Tool](#) at the end of this report.

Impact on Guidelines and Its Recommendations

The new data did not change the existing recommendations for IL-2 in the treatment of patients with unresectable or metastatic renal cell carcinoma. Hence, the Genitourinary Cancer DSG **ENDORSED** the 2006 recommendations.

Education and Information



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Evidence-Based Series 3-8-2: Section 1

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer: A Clinical Practice Guideline

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Please see the EBS 3-8-2 Guideline Review [Summary](#)
and the [Document and Assessment Review Tool](#)
for the summary of updated evidence published between 2005 and 2010.

Report Date: June 8, 2006

Question

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

Recommendations

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

Qualifying Statements

- Patients with unresectable or metastatic 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 RCC. These

approaches show modest survival benefits in randomized trials and may be considered treatment options in this patient population.

- High-dose IL-2 has not been compared to appropriate comparators using non-IL-2-containing regimens in randomized trials, and so its effectiveness is unclear. Despite this, high-dose IL-2 is being used as a standard treatment for unresectable or metastatic RCC in much of the United States and parts of Europe based on single-arm studies.

Key Evidence

- Six randomized trials comparing IL-2-containing regimens to regimens without IL-2 form the evidence base of this review. Three trials had three arms, and three trials had two arms, providing a total of nine comparisons. Patient accruals ranged from 60 to 425 and totalled 1,098 eligible randomized patients. Each trial assessed IL-2 combined with other agents, and two of three three-arm trials also assessed IL-2 as a single agent. IL-2 was studied in combination with interferon-alpha in each trial, either alone or with chemotherapy (e.g., fluorouracil or 5-fluorouracil) and 13-cis-retinoic acid or tamoxifen. No trials were identified that compared high-dose IL-2 to non-IL-2 regimens.
- Objective response rate was the primary outcome in four trials but was reported in five of six trials. Other outcomes assessed included overall survival (six trials), progression-free survival (four trials), and toxicity (six trials). Quality of life data were not reported in any of the trials.
- 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 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 (RR=0.56; 95% CI, 0.38-0.82; p=0.003); however, those trials have some methodological limitations.
- Toxicity data were described in all six trials. IL-2-based regimens were generally more toxic than non-IL-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.

Related Guidelines

- Evidence-based Series #3-8-1: *The Use of Interferon-alpha for the Treatment of Patients with Locally Advanced or Metastatic Renal Cell Cancer (in progress).*
- Evidence-based Series #3-8-3: *The Role of Cytoreductive Nephrectomy in the Management of Patients Treated with Immunotherapy for Metastatic Renal Cell Cancer.*

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Evidence-Based Series #3-8-2: Section 2

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer: A Systematic Review

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Please see the EBS 3-8-2 Guideline Review [Summary](#)
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Report Date: June 8, 2006

QUESTION

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

INTRODUCTION

Renal cell carcinomas account for three percent of all adult solid malignancies (1). It is estimated that, in 2004, 4,300 patients were diagnosed with the disease in Canada (2). At the time of first diagnosis, 45% of patients will present with localized disease, 25% will have locally advanced disease with lymph node or local organ involvement, and the remaining 30% will present with metastases (3). Patients with metastatic disease have a five-year life expectancy of less than 10% and a median survival time of less than 12 months. However, survival can be quite variable depending on a number of prognostic factors, including performance status, lactate dehydrogenase (LDH), hemoglobin, calcium levels, and the absence of prior nephrectomy (4).

For patients presenting with inoperable or metastatic disease, cure is rarely possible, and treatment efforts often center on effectively controlling symptoms and offering a chance at improved survival. Clinical trials of chemotherapy in the metastatic setting have shown RCC to be resistant to currently available chemotherapeutic agents (5). Immunotherapy agents, however, have shown activity in RCC. The interleukins are a family of polypeptides originally named for their ability to mediate interactions between leucocytes. Initially called

T-cell growth factor, IL-2 was recognized as a product of activated T-cells that stimulates the proliferation and enhances the function of other T-cells and such immunocompetent cells as natural killer (NK) cells and B-cells (6). IL-2 has been evaluated extensively in the setting of advanced RCC, using various doses and modes of delivery in order to try and maximize efficacy and decrease the significant toxicities that can be associated with high-dose IL-2 therapy. Such toxicities include profound hypotension and cardiovascular collapse. Because of the potentially serious and frequent toxicities of IL-2, a large number of clinical trials have been conducted. Unfortunately, and without obvious reason other than perhaps the fact that advanced RCC is reasonably uncommon and that until recently, very few research groups concentrated their efforts on conducting large trials in this type of cancer, no large, properly powered randomized trials have ever been conducted to answer the clinical question of whether IL-2 improves survival in patients with advanced RCC. Instead, a large number of smaller trials using multiple dose frequencies and concentrations, and in combination with many different other agents have been conducted. Furthermore, the comparator arms chosen have also been very disparate. For all these reasons, it has been difficult to assess the true clinical benefit of IL-2.

High-dose IL-2 was approved by the United States (US) Federal Drug Administration in 1992, based on the pooled results of seven phase II studies conducted in 21 separate institutions (7). In these series, 15% of patients (37/255, 17 complete and 20 partial responses) achieved an objective response, and the median duration of response among the objective responders was 54 months. The median survival of all 255 patients was 16.3 months. No randomized controlled trials (RCTs) using appropriate comparators (i.e., non-IL-2-containing regimens) have been conducted to confirm the benefits associated with high-dose IL-2.

There is currently no universally accepted standard of care for patients with advanced RCC. Since its approval in the US, high-dose IL-2 has been used in patients with advanced RCC with reasonable frequency. The approval of this treatment option as the US standard has likely contributed to the small number of trials without an IL-2 arm; a belief in this treatment makes recruitment into trials studying other agents difficult or even unethical. In Canada, IL-2 was also approved by Health Canada in 2003 but as opposed to the US, the use of high-dose IL-2 has varied greatly. Because of its modest survival improvement, most consider interferon-alpha the standard of care in Canada, as it is the most widely used immunotherapeutic agent.

The purpose of this report was to systematically review evidence from RCTs of IL-2 in unresectable or metastatic RCC in order to develop appropriate guidelines for treatment. Multiple regimen schedules, doses, and types of immunotherapy have been studied in combination with and in comparison to IL-2, making a direct assessment of the potential efficacy of IL-2 difficult. For this reason, only RCTs comparing IL-2-based regimens to regimens without IL-2 were considered.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC). Evidence was selected and reviewed by four members of PEBC's Genitourinary Cancer Disease Site Group (GU DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on IL-2 for unresectable or metastatic RCC. The body of evidence in this systematic review is primarily comprised of mature RCT data; it forms the basis of a clinical practice guideline developed by the GU DSG and published elsewhere. This systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario,

Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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 "interleukins"; 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", "immunotherap:", "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 Guidelines Clearing house (<http://www.guideline.gov/index.asp>) 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 RCTs or meta-analyses of RCTs comparing IL-2-containing treatment regimens to regimens without IL-2 in patients with unresectable or metastatic 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-RCC patients were eligible as long as the outcomes for RCC patients were analyzed separately. Existing systematic reviews or evidence-based practice guidelines relevant to the guideline question were also eligible. RCTs that compared either surgery or radiotherapy with IL-2 immunotherapy were excluded.

Synthesizing the Evidence

Objective Response Rate

To estimate the overall effect of IL-2-based immunotherapy on response rate compared with non-IL-2 regimens, the response rates from individual RCTs were pooled and weighted according to the size of the treatment arms using the following formula (8):

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

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 RCTs 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 (9). 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^2 (values of 25%, 50%, and 75% indicate low, moderate, and high degrees of heterogeneity) statistics (10).

RESULTS

Literature Search Results

Thirty-six unique RCTs of IL-2 were identified by the literature search (11-48) and seven of those met the eligibility criteria of this review (12,13,19,25,26,29,38). A table of ineligible trials with explanations of exclusions is available in Appendix 1. One of the seven eligible trials was excluded because a majority of patients (58%) were lost to follow-up (13), leaving six trials for inclusion (12,19,25,26,29,38). All six trials were published as full reports in journals. Three systematic reviews with meta-analyses were also identified (49-51); two of those were excluded because they pooled data from both randomized and non-randomized clinical trials (50,51). No evidence-based guidelines were identified.

Previous Systematic Review with Meta-analysis

In 2000, Coppin et al published a Cochrane systematic review on immunotherapy for inoperable or metastatic RCC. In 2005, the review was updated to cover the literature through to December 2003 and include 12 new trials and updated results to five trials included in the 2000 review (49). The review examined the efficacy of a range of immunotherapies including IL-2. Eligible reports were RCTs examining any immunotherapy in at least one trial arm that reported results on mortality and/or remission by treatment arm. Meta-analyses were performed for both outcomes using data available from published trial reports, and treatment comparisons were specified a priori. Three comparisons evaluated in

the Cochrane review (as subgroup analyses) met the criteria of this review (i.e., compared IL-2-based regimens to non-IL-2 regimens) and include the following:

- 1) high-dose IL-2 vs. non-IL-2 controls,
- 2) IL-2 plus IFN-a vs. IFN-a alone, and
- 3) IL-2-based regimens vs. IFN-a alone.

High-dose IL-2 was defined by the authors as IL-2 administered as an intravenous bolus of at least 600,000 IU/kilogram every eight hours, or a dose exceeding 65 MU/m² per day. No trials were identified that addressed comparison 1. The meta-analysis results for comparisons 2 and 3 are summarized in Table 1 and were expressed as odds ratios (reported with 95% CI) analyzed using a fixed effects model. An OR <1.0 indicates an IL-2 benefit and an OR of >1.0 indicates a non-IL-2 benefit.

Table 1: Selected results from the Coppin et al. 2005 Cochrane systematic review and meta-analysis.

Outcome	Trials† contributing to pooled estimate (reference)	No. of events	Results OR (95% CI), p-value
Comparison 2: IL-2 + IFN-a vs. IFN-a			
Mortality at 1-year	Boccardo 1998 (25) Negrier 1998 (29)	10/22 vs. 6/21 49/140 vs. 60/147	0.89 (0.57-1.38), p=0.6
Remission*	Boccardo 1998 (25) Negrier 1998 (29)	2/22 vs. 2/22 26/140 vs. 9/138	2.65 (1.36-5.16), p=0.004
Comparison 3: IL-2-based regimens vs. IFN-a			
Mortality at 1-year	Boccardo 1998 (25) Negrier 1998 (29)	6/21 vs. 5/22 61/138 vs. 60/147	1.17 (0.75-1.82), p=0.5
Remission*	Boccardo 1998 (25) Negrier 1998 (29)	5/22 vs. 2/22 9/138 vs. 11/147	1.14 (0.52-2.5), p=0.7

Abbreviations: CI - confidence interval, IL-2 - interleukin-2, IFN-a - interferon-alpha, No. - number, OR - odds ratio, vs. - versus.

*Remission is defined as the number of patients achieving a partial or complete response.

†Both trials (Boccardo 1998 and Negrier 1998) are three-arm trials providing two comparisons.

The meta-analysis results described above are all based on subgroup analyses and are limited by the inclusion of a small number of trials and patients. Further, the trial by Negrier et al (29) is much larger than the Boccardo et al trial (25) and therefore contributes the most to each analysis. Therefore, it is likely little is gained by combining the results of the two trials, and the pooled results should be interpreted with caution. Results from the meta-analyses show no differences between IL-2-based regimens and non-IL-2 regimens in both one-year mortality and remission. IL-2 combined with IFN-a was associated with a statistically significant improvement in remission compared to IFN-a alone (odds ratio [OR]=2.65; 95% CI, 1.36-5.16; p=0.004], but that did not translate into an improvement in survival at one year (OR=0.89; 95% CI, 0.57-1.38; p=0.6).

In total, Coppin et al (49) reviewed 22 trials of IL-2 (16,19-21,24-29,34,38-41,43,45,47,48,52-54) and evaluated the following additional comparisons involving IL-2:

- high-dose IL-2 vs. reduced dose IL-2,
- IL-2 with or without LAK cells or tumour-infiltrating lymphocytes,
- IL-2 plus IFN-a vs. IL-2 alone,
- IL-2 and IFN-a with or without an enhancer,
- combination immunochemotherapy vs. control, and

- high-dose IL-2 vs. reduced-dose IL-2 plus IFN-a.

From their review of the 22 trials, Coppin et al concluded that because high-dose IL-2 has not been compared to other therapy, its possible superiority must be based on the results of phase II studies, which were not reviewed in the Cochrane overview. They also concluded that modified or reduced schedules of IL-2 should not be recommended to patients with inoperable or metastatic RCC outside of clinical trials until studies with adequate patient numbers show greater efficacy than IFN-a, or equivalence with less toxicity.

Randomized Controlled Trials

Trial Characteristics

The six trials that form the basis of this review were published between 1996 and 2004 (Table 1). There were three three-arm trials (12,25,29) and three two-arm trials (19,26,38). Across those trials, a total of 1,098 eligible patients were randomized, with patient accruals per trial ranging from 60 to 425. None of the trials were placebo-controlled. All the trials assessed IL-2 in combination with other agents, while two of the three three-arm trials also included a single-agent IL-2 arm (25,29). IL-2 was studied in combination with interferon-alpha (IFN-a2a or 2b) in each trial, either alone (25,29,38) or with chemotherapy (i.e., fluorouracil, 5-fluorouracil) (12,19) and 13-cis retinoic acid (12) or tamoxifen (26). Doses and modality of administration of IL-2 differed significantly between trials. Four trials evaluated IL-2 given subcutaneously (two at a low dose of 2.4 to 4.8 MU/m²), and two trials evaluated IL-2 administered intravenously at doses of 5.0 to 10.0 MU/m². The median age of patients ranged from 57 to 62 years, and the majority of patients were male (range, 59 to 82%) with good performance status (i.e., Karnofsky >80%, WHO or ECOG ≤2). The median follow-up of patients across the six trials was 22 months (range, 11 to 39).

Data indicative of trial quality, including methods of randomization and allocation concealment, adequacy of the description of trial arms, whether analyses included all randomized patients, and completeness of follow-up, were reviewed for each trial. Four of the six trials reported the method of randomization used (12,19,26,29); each of those described stratified randomization procedures. All the trials presented baseline demographic and clinical characteristics for treatment and control arms, and four stated that randomization achieved balance in the distribution of those characteristics between arms (12,19,25,29). The method of allocation concealment was not reported in any of the trials, and none of the trials were blinded. Five trials reported the percentage of patients receiving intended treatment and withdrawing from study (12,19,25,26,29), and all employed an intent-to-treat approach to statistical analyses. A crossover trial design was used in three trials (12,19,29); in each of those, patients crossed over to alternative therapy upon disease progression after eight (12,19) or 10 weeks (29) of assigned treatment.

Table 2: Randomized trials of interleukin-2-containing regimens vs. regimens without interleukin-2 in patients with unresectable or metastatic renal cell cancer: trial descriptions.

Trial	Treatment arms (dose & route)	No. patients randomized/evaluable
Atzpodien 2004 (12)	A: IFN-a2a (5–40MU/m ² sc), IL-2 (10–5MU/m ² sc), FU (1000mg/m ² iv) B: IFN-a2a (5–40MU/m ² sc), IL-2 (10–5MU/m ² sc), FU (1000mg/m ² iv), 13cRA (20mg po) C: IFN-a2a (5–40MU/m ² sc), VBL (6mg/m ² iv)	341/341
Atzpodien 2001 (19)	A: IL-2 (10–5MU/m ² sc), IFN-a (5–40MU/m ² sc), 5-FU (1000mg/m ² iv) B: Tamoxifen (80mg po)	78/78
Boccardo 1998 (25)	A: IL-2 (18MU/m ² iv) B: IL-2 (18MU/m ² iv), IFN-a2a (6MU/m ² im) C: IFN-a2a (6MU/m ² im)	66/66
Henriksson 1998 (26)	A: IL-2 (4.8–2.4MU/m ² sc), IFN-a (3–6MU/m ² sc), tamoxifen (40mg po) B: Tamoxifen (40mg po)	128/128
Negrier 1998 (29)	A: IL-2 (18MU/m ² iv) B: IL-2 (18MU/m ² iv), IFN-a2a (6MU/m ² sc) C: IFN-a2a (18MU/m ² sc)	425/425
Lummen 1996 (38)	A: IL-2 (4.8–2.4MU/m ² sc), IFN-a2b (3–6MU/m ² sc) B: IFN-γ (200μg sc)	60/60

Abbreviations: 5-FU - 5-fluorouracil, FU - fluorouracil, IL-2 - interleukin-2, im - intramuscular, IFN-a - interferon-alpha, IFN-γ - interferon-gamma, iv - intravenous, m² - metres squared, mg - milligrams, ml - millilitres, MU - million units, No. - number, po - per oral, sc - subcutaneous, VBL - vinblastine.

Outcomes

The results of the six RCTs are summarized by outcome in Tables 3 and 4. Objective response rate was designated the primary outcome in four trials (12,19,25,29) but was reported in five trials (12,19,25,29,38) (Table 3). Overall survival and progression-free survival data were reported in six and four trials (12,19,25,29), respectively (Table 3). All six trials reported toxicity data (12,19,25,26,29,38) (Table 4). Quality of life data were not reported in any of the trial reports.

Objective Response Rate

Three of the five trials reporting objective response were three-arm trials providing two comparisons of IL-2-based immunotherapy, giving a total of eight comparisons among the five trials. Only three trials provided statistical comparisons of those data (12,29,38); two trials (three comparisons) reported higher response rates with IL-2 that were statistically significant (29,38). Negrier et al (29) reported an objective response rate of 18.6% with combination IL-2 and IFN-a2a versus 7.5% ($p<0.01$) and 6.5% ($p<0.01$) with single-agent IFN-a2a and single-agent IL-2, respectively. Statistical findings were not reported for the comparison of IL-2 versus IFN-a2a. Lummen et al (38) also reported a higher objective response rate with combination IL-2 and IFN-a2b over IFN-gamma (23% vs. 0%, $p=0.01$). In the two trials for which statistical comparisons were not provided, response rates favoured IL-2-based therapy compared with tamoxifen in the trial by Atzpodien et al (19), and Boccardo et al (25) reported a better response rate with single-agent IL-2 versus both single-agent IFN-a2a

and combined IFN- α 2a/IL-2. When the objective response rates from the five trials were combined, the overall weighted objective response rates for IL-2-containing regimens versus non-IL-2 regimens were 13.3% (range, 9 to 39%) versus 5.3% (range, 0 to 20%).

Survival

All six trials reported survival data (nine comparisons) (Table 3). Median survival data were reported in four trials (12,19,26,29) and extracted from survival curves in two trials (25,38). Five of the six trials provided statistical comparisons for median survival times between trial arms (12,19,26,29,38). Two of those reported statistically significant survival improvements with IL-2-based immunotherapy (12,19). In the trial by Atzpodien et al (12), median survival was longer for patients treated with combination IL-2/IFN- α with either fluorouracil (25 months; $p=0.04$) or 13-cis-retinoic acid (27 months; $p=0.02$) compared to patients receiving combined treatment with IFN- α 2a and vinblastine (16 months). In the other trial by Atzpodien et al (19), a statistically significant longer median survival was observed with IL-2 combined with IFN- α and 5-fluorouracil over tamoxifen (24 versus 13 months; $p=0.03$).

One-year mortality data were reported in one trial (26) and extracted from survival curves in five trials (12,19,25,26,29) (Table 3). 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 (RR=0.94; 95% CI, 0.67-1.30; $p=0.69$) (Figure 1). Statistically significant heterogeneity was detected across the six trials ($p=0.003$, $I^2=71.7\%$) and was therefore explored through a sensitivity analysis. Visual inspection of the meta-analysis figure clearly identified the two trials by Atzpodien et al (12,19) as the likely source of heterogeneity. Both trials evaluated immunochemotherapy (IL-2-based regimens with either 5-fluorouracil or fluorouracil), and each detected a statistically significant survival improvement with those regimens over control therapy. When both trials were removed from the meta-analysis the overall result remained the same (RR=1.20; 95% CI, 1.00-1.44; $p=0.06$) but heterogeneity was no longer statistically significant ($p=0.81$, $I^2=0\%$). The subgroup of the two Atzpodien et al trials (12,19) showed a statistically significant reduction in one-year mortality with immunochemotherapy (RR=0.56; 95% CI, 0.38-0.82; $p=0.003$).

Table 3: Randomized trials of interleukin-2-containing regimens vs. regimens without interleukin-2 in patients with unresectable or metastatic renal cell cancer: outcomes.

Trial	Treatment Arms (n)	Objective Response Rate %				Median in mos	Survival p-value*	1-yr %	5-yr %	Progression-free Survival* Median in mos	Survival* p-value*
		OR	CR	PR	p-value*						
Atzpodien 2004 (12)	A: IFN-a2a/IL-2/FU (132)	31	5	26	NS	25	p=0.04	76.5†	16.1†	6	p=0.025 B vs. C
	B: IFN-a2a/IL-2/FU/13cRA (146)	26	8	18	A vs. B, C	27	p=0.02	70.5†	22.3†	7	
	C: IFN-a2a/VBL (63)	20	6	14		16		58.9†	19.6†	5	
Atzpodien 2001 (19)	A: IL-2/IFN-a/5-FU (41)	39	17	22	NR	24	p=0.03	80†	24.8	7	p<0.0001
	B: Tamoxifen (37)	0	0	0		13		52†	13.5	0	
Boccardo 1998 (25)	A: IL-2 (22)	23	9	14	NR	28.3†	NR	70†	NA	9.6†	NR
	B: IL-2/IFN-a2a (22)	9	4.5	4.5		13.3†		56.5†		5.1†	
	C: IFN-a2a (22)	9	0	9		17.6†		76†		6.4†	
Henriksson 1998 (26)	A: IL-2/IFN-a/tamoxifen (65)	NR	7.7	NR	NR	11.8	NS	40	NA	NR	
	B: Tamoxifen (63)		3			13.3		48			
Negrier 1998 (29)	A: IL-2 (138)	6.5‡	1.4‡	5.1‡	p<0.01 B vs. A, C	12	NS B vs. A, C	56.8†	NA	15 (PFS 1yr)	p=0.01 B vs. A, C
	B: IL-2/IFN-a2a (140)	18.6‡	<1‡	18‡		17		60.2†		20 (PFS 1yr)	
	C: IFN-a2a (147)	7.5‡	0‡	7.5‡		13		66.3†		12 (PFS 1yr)	
Lummen 1996 (38)	A: IL-2/IFN-a2b (30)	23	10	13	p=0.01	12	p=0.49	50†	NA	NR	
	B: IFN-γ (30)	0	0	0		13		54†			

Abbreviations: CR - complete response, 13cRA - 13-cis-retinoic acid, 5-FU - 5-fluorouracil, FU - fluorouracil, IL-2 - interleukin-2, IFN-a - interferon-alpha, IFN-γ - interferon-gamma, mos - months, NA - not available, NR - not reported, NS - non-significant, OR - objective response, PFS - progression-free survival, po - per oral, PR - partial response, TTP - time-to-progression, VBL - vinblastine, vs. - versus, yr - year.

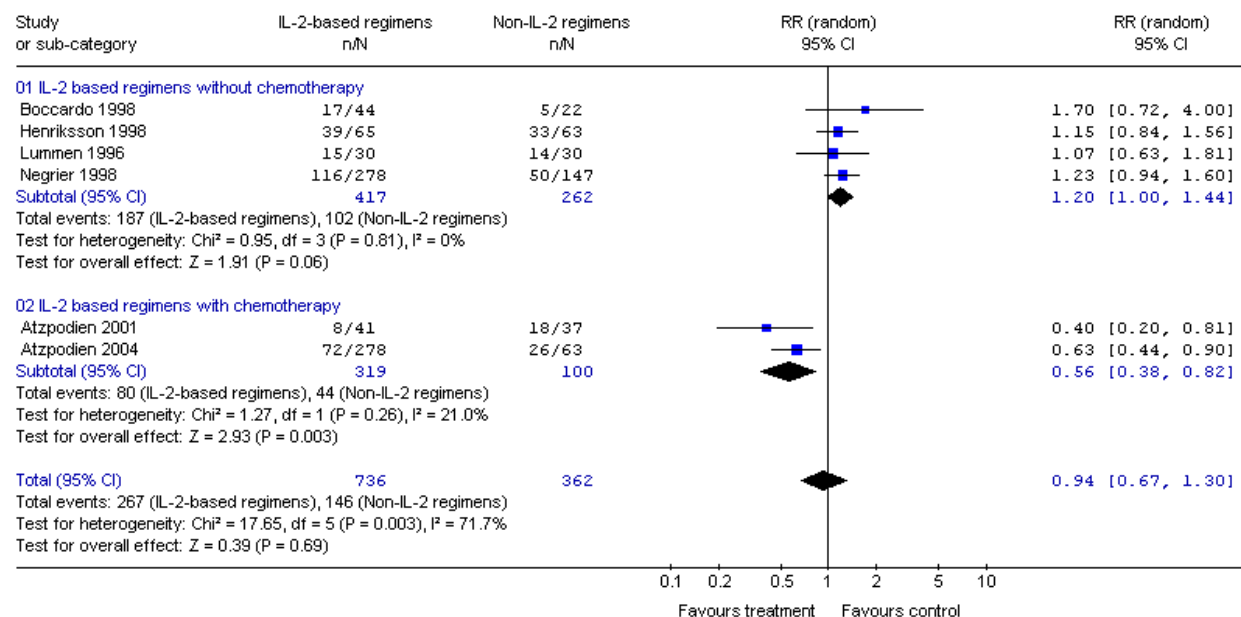
*Only statistically significant differences are presented.

†Data extracted from survival curve.

‡Response at 10 weeks after induction treatment.

Figure 1. Meta-analysis of 1-year mortality data from trials of interleukin-2 containing regimens vs. regimens without interleukin-2 in patients with unresectable or metastatic renal cell cancer.

Comparison: 01 IL-2 based regimens vs. regimens without IL-2
Outcome: 01 Mortality at 1-year



Disease Progression

Four of the six trials assessed progression-free survival (12,19,25,29) (Table 3). Three of the trials reported statistical comparisons (12,19,29), and each of those detected longer progression-free intervals with IL-2-based regimens over non-IL-2 controls that were statistically significant. In the largest of those trials (29), median progression-free survival at one year was significantly longer for patients treated with IL-2 combined with IFN- α 2a (20 months) compared with single-agent IL-2 (15 months; $p=0.01$) and single-agent IFN- α 2a (12 months; $p=0.01$).

Toxicity

All six trials reported on toxicity; however, grade 3 or 4 toxicity data were described in five of the six trials (12,19,25,26,29) (Table 4). Overall, IL-2-containing regimens appeared more toxic than non-IL-2 regimens but were described as moderately to well tolerated by most patients in the majority of trials. In two trials, IL-2-based immunotherapy was administered in an outpatient setting (12,19). The majority of toxicities were graded as 1 or 2 (data not shown), but grade 3 or 4 toxicity was observed in a substantial number of patients. The most common grade 3 or 4 toxicities associated with IL-2-based treatment were 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%). Only two trials reported on toxicity-related dose reductions or treatment discontinuations. Dose reductions occurred in 7% of patients treated with combination IL-2, IFN- α and 5-fluorouracil compared to none with tamoxifen (19). The toxicity of combination IL-2/IFN- α /fluorouracil and IL-2/IFN- α /fluorouracil/13-cis-retinoic acid caused treatment discontinuations in 4% and 6% of

patients, respectively, compared with 8% in patients treated with IFN- α /vinblastine (12). No toxic deaths were reported in two trials reporting those data (12,19).

Table 4: Randomized trials of interleukin-2-containing regimens vs. regimens without interleukin-2 in patients with unresectable or metastatic renal cell cancer: reported toxicity.

Trial	Treatment Arms	Reported Grade 3/4 Toxicity, % of patients	Reported No. of Toxic Deaths
Atzpodien 2004 (12)	A: IFN- α /IL-2/FU	Fever (3), chills (3), malaise (3), diarrhea (3), respiratory distress (3), skin or allergies (3), hemoglobin levels (4)	0
	B: IFN- α /IL-2/FU/13cRA	Fever (3), chills (6), malaise (18), nausea or vomiting (6), anorexia (21), diarrhea (3), respiratory distress (3), skin or allergies (2), mucositis (3), hypotension (6), alopecia (3), arrhythmias (3), paresthesias (3), leucocyte count (3)	0
	C: IFN- α /VBL	Malaise (11), anorexia (26), CNS or disorientation (11)	0
Atzpodien 2001 (19)	A: IL-2/IFN- α /5-FU	Fever (2), chills (3), malaise (7), diarrhea (1), dyspnea (1)	0
	B: Tamoxifen	None reported	0
Boccardo 1998 (25)	A: IL-2	Oliguria (17), hypotension (28), skin rash (11), fever (11), creatinemia (6), neurological toxicity (11), cardiac toxicity (11), diarrhea (17), nausea/vomiting (6)	NR
	B: IL-2/IFN- α 2a	Oliguria (19), hypotension (38), skin rash (6), fever (25), cardiac toxicity (25), diarrhea (19), nausea/vomiting (19), thrombocytopenia (6)	
	C: IFN- α 2a	Oliguria (6), hypotension (6), asthenia (11)	
Henriksson 1998 (26)	A: IL-2/IFN- α /tamoxifen	Fatigue (58), anorexia (22), nausea (22), fever (12), diarrhea (8), myalgia (18), pulmonary (14), infection (3), cutaneous (<2), headache (3), oral (<2), CNS (<2)	NR
	B: Tamoxifen	Fatigue (30), anorexia (11), nausea (8), diarrhea (3), myalgia (22), pulmonary (17), oral (<2), CNS (<3)	
Negrier 1998 (29)	A: IL-2	Hypotension (68), fever (43), performance status impairment (36), nausea/vomiting (34), diarrhea (28), anemia (17), pulmonary symptoms (16), renal symptoms (15), neurologic symptoms (12), increased AST or ALT (11), cutaneous signs (10), cardiac signs (12), infection (8), thrombocytopenia (4), increased creatinine (4), weight loss (2), leucopenia (<1), hyperbilirubinemia (<1)	NR
	B: IL-2/IFN- α 2a	Hypotension (67), fever (56), performance status impairment (38), nausea/vomiting (31), diarrhea (25), anemia (16), pulmonary symptoms (15), renal symptoms (16), neurologic symptoms (14), increased AST or ALT (11), cutaneous signs (14), cardiac signs (6), infection (9), thrombocytopenia (7), increased creatinine (5), weight loss (1), leucopenia (2), hyperbilirubinemia (2)	
	C: IFN- α 2a	Hypotension (<1), fever (5), performance status impairment (16), nausea/vomiting (5), diarrhea (<1), anemia (6), pulmonary symptoms (3), neurologic symptoms (1), increased AST or ALT (3), cardiac signs (<1), infection (<1), weight loss (4), leucopenia (<1)	
Lummen 1996 (38)	A: IL-2, IFN- α 2b	None	NR
	B: IFN- γ	None	

Abbreviations: 13-cis-retinoic acid, CNS - central nervous system, 5-FU - 5-fluorouracil, FU - fluorouracil, IL-2 - interleukin-2, IFN- α - interferon-alpha, IFN- γ - interferon-gamma.

DISCUSSION

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.

This review identified 34 trials that evaluated IL-2. Of those, only six met the inclusion criteria. The main reason for the large attrition proportion is that the majority of trials did not contain an arm without IL-2. The six eligible RCTs evaluated IL-2 in modified doses, either intravenously or subcutaneously, in comparison to a variety of regimens. None evaluated high-dose IL-2. Response rates appeared improved in patients receiving IL-2-based regimens (range, 6.5-39%) compared with non-IL-2 controls (0-20%). All six trials reported mortality data, and when the six trials were pooled in a meta-analysis, mortality at one-year was not significantly different between IL-2-based regimens and non-IL-2 regimens. These observations are consistent with those of Coppin et al (49), who identified that objective response rate does not serve as a particularly reliable surrogate for survival benefit in RCC. A sensitivity analysis showed IL-2-based regimens with chemotherapy (5-fluorouracil, fluorouracil) were associated with a statistically significant reduction in one-year mortality over non-IL-2 controls. However, features of these trials warrant that those immunochemotherapy regimens be further investigated in randomized trials before being considered standard treatment.

The 2001 Atzpodien et al trial (19), which showed the largest treatment effect, was a small trial (n=78) and therefore should not be considered definitive proof of efficacy. There were also imbalances in important prognostic variables (e.g., age and possibly performance status) between trial arms that may have influenced outcomes resulting in a bias towards the tamoxifen control arm. The 2004 Atzpodien et al trial (12) was better powered to detect differences between arms (n=341), and appeared well balanced with the exception of a higher percentage of patients with metastases and non-nephrectomized patients in the control arm. However, only favourable risk patients were recruited into the trial, which raises concern over generalizing the results to the general population of patients with metastatic RCC, especially since previous trials studying these cytokine combinations have failed to show survival benefits. Further limitations of the trial are discussed in an editorial by Negrier that accompanied the published trial report (55); it also concludes the findings of the trial should be interpreted with caution and validated in a rigorous controlled trial before they be considered reference treatment for future trials.

Overall, toxicity appeared worse with IL-2-based therapy than for non-IL-2 therapy; however, most studies described IL-2 regimens as moderately to well-tolerated by most patients. Toxicities such as hypotension, cardiac toxicity, diarrhea, and fatigue appeared particularly increased when compared to IFN- α or other treatment arms. No toxic deaths were reported, and quality of life data were not reported in any of the trials. It is generally felt that IL-2-based regimens are associated with significant toxicity and the magnitude of this toxicity may be underestimated in clinical trials due to patient selection factors.

This review did not identify any randomized trials comparing high-dose intravenous IL-2 to a non-IL-2 control or placebo, and so its effectiveness remains unclear. For this reason, it is impossible to recommend its use outside of clinical trials or investigational settings. High-dose IL-2 is currently the standard of care in the United States and in parts of Europe, based on phase II clinical trials. A published series by Fisher et al (7) combining data from seven non-randomized, single-arm phase II trials suggests that a minority of patients can experience complete and long-lasting remissions with high-dose IL-2. That series suffers from the lack of a control arm, which can suggest a treatment effect when one actually does not exist. Furthermore, high-dose IL-2 was very resource-intensive (most required intensive care unit [ICU] admission for administration) and had a significant toxicity profile. The small

proportion of patients who experience long-lasting remissions is intriguing and efforts should be pursued to better delineate this subpopulation *a priori* to maximize benefit in those patients and minimize toxicity to patients who are unlikely to benefit.

Randomized trials of IFN- α -based immunotherapy, as well as cytoreductive nephrectomy combined with INF- α , have shown modest survival benefits in this patient population and therefore may be considered as treatment options. Both of those topics are covered in separate guidelines being developed by the GU DSG.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The GU DSG will monitor the progress of the following trials and review reported results when they become available.

Protocol ID(s)	Title and details of trial
MRC - RE04, EU-20231, ISRCTN46518965, NCT00053820, EORTC-30012	Phase III randomized study of interferon-alpha with or without interleukin-2 and fluorouracil in patients with advanced metastatic renal cell carcinoma. Treatment groups: interferon-alpha vs. interferon-alpha/interleukin-2/fluorouracil Target accrual: 670 Date trial summary last modified: December 20, 2004 Status: active

CONCLUSIONS

In patients with unresectable or metastatic RCC, IL-2-containing immunotherapy does not provide superior treatment efficacy over non-IL-2 regimens, with added toxicity. There is evidence that IL-2 combined with IFN- α and chemotherapy (5-fluorouracil, fluorouracil) improves response rates and survival when compared to either agent alone or a non-immunotherapy control; however, those findings require confirmation in further, properly powered clinical trials with appropriate comparators (i.e., IFN- α) and should not be considered the standard of care. There are insufficient data to support the routine use of high-dose intravenous IL-2 therapy outside of a clinical trial or investigational setting, and its unique toxicity warrants its administration in specialized centres equipped to deal with specific toxicities and provide comprehensive care.

CONFLICT OF INTEREST

The members of the GU DSG disclosed potential conflicts of interest relating to this systematic review and none were declared.

JOURNAL REFERENCE

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Appendix 1: Ineligible trials.

Trial (reference)	Reason for Exclusion
McDermott 2005 (11)	IL-2 in all arms
Brinkmann 2004 (13)	58% of patients lost to follow-up
Peterson 2004 (14)	IL-2 in all arms
Smith 2003 (15)	IL-2 in all arms
Yang 2003 (16)	IL-2 in all arms
Mansoor 2003 (17)	IL-2 in all arms
Phan 2002 (18)	IL-2 in all arms
Lissoni 2000 (20)	IL-2 in all arms
Negrier 2000 (21)	IL-2 in all arms
Tourani 2000 (22)	IL-2 in all arms; maintenance trial
Urba 2000 (23)	IL-2 in all arms
Figlin 1999 (24)	IL-2 in all arms
Jayson 1998 (27)	IL-2 in all arms
Naglieri 1998 (28)	IL-2 in all arms
Cormier 1997 (30)	IL-2 in all arms; unstratified mixed melanoma/renal cell trial
Dubois 1997 (31)	IL-2 in all arms; unstratified mixed melanoma/renal cell trial
Dutcher 1997 (32)	IL-2 in all arms; mixed randomized and non-randomized outcome data
Margolin 1997 (33)	IL-2 in all arms; unstratified mixed melanoma/renal cell trial
Scardino 1997 (34)	Surgery in all arms
Ahmed 1996 (36)	IL-2 in all arms; unstratified mixed melanoma/renal cell trial
Fenton 1996 (37)	Surgery in all arms
Law 1995 (39)	IL-2 in all arms
Witte 1995 (40)	IL-2 in all arms
Yang 1995 (41)	IL-2 in all arms
Lissoni 1993 (43)	IL-2 in all arms
Lissoni 1993 (44)	IL-2 in all arms; maintenance therapy as randomized variable
Rosenberg 1993 (45)	IL-2 in all arms
Leahy 1992 (46)	IL-2 in all arms; unstratified mixed tumour trial
Weiss 1992 (47)	IL-2 in all arms
McCabe 1991 (48)	IL-2 in all arms

Abbreviations: IL-2 - interleukin-2.



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Evidence-Based Series #3-8-2: Section 3

Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer: Guideline Development and External Review - Methods and Results

*S. Hotte, T. Waldron, C. Canil, E. Winquist, and members of the Genitourinary
Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Please see the EBS 3-8-2 Guideline Review [Summary](#)
and the [Document and Assessment Review Tool](#)
for the summary of updated evidence published between 2005 and 2010.

Report Date: June 8, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series:

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review - Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Genitourinary Cancer DSG (GU DSG) of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on IL-2 for unresectable or metastatic 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. For a current list of GU DSG members please visit <http://www.cancercare.on.ca/>.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the 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 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 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 RCC.
- *Minor editorial changes.* The GU DSG made suggested editorial changes.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series, the GU DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

Box 1:**DRAFT RECOMMENDATIONS** (approved for external review April 26, 2006)***Recommendation***

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

Qualifying Statements

- Patients with unresectable or metastatic 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 RCC. These approaches show modest survival benefits in randomized trials and may be considered treatment options in this patient population.
- High-dose IL-2 has not been compared to appropriate comparators using non-IL-2-containing regimens in randomized trials, and so its effectiveness is unclear. Despite this, high-dose IL-2 is being used as a standard treatment for unresectable or metastatic RCC in much of the United States and parts of Europe based on single-arm studies.

Methods

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.

Results

Thirty-nine responses were received out of the 92 surveys sent (42% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 67% indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	25 (96.2)	1 (3.8)	0
There is a need for a guideline on this topic.	23 (88.5)	1 (3.8)	2 (7.6)
The literature search is relevant and complete.	22 (84.6)	3 (11.5)	1 (3.8)
The results of the trials described in the report are interpreted according to my understanding of the data.	25 (96.1)	0	1 (3.8)
The draft recommendations in the report are clear.	26 (100)	0	0
I agree with the draft recommendations as stated.	23 (88.4)	0	3 (11.5)
This report should be approved as a practice guideline.	20 (77)	3 (11.5)	3 (11.5)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	18 (72)	2 (8)	5 (20)

Summary of Written Comments

Five respondents (19%) provided written comments. The main points contained in the written comments were:

1. Three urologists indicated that they do not administer chemotherapy, and patients they see with unresectable metastatic RCC are referred to an oncologist.
2. One practitioner suggested phase II trials be included in the report because of the limited evidence and the small number of patients included in the randomized trials of IL-2.
3. One practitioner commented that some patients benefit from high-dose IL-2 but prior identification of these patients is not possible at this time. Patients need to be entered onto trials of IL-2 but this agent is not available for study in Ontario. Further, this field of study is changing with the use of sorafenib and sunitinib.

Modifications/Actions

1. Regarding the comment about inclusion of phase II trials - at the onset of developing the systematic review, the GU DSG set specific inclusion and exclusion criteria. They decided a priori to exclude phase II studies from the review due to the biases associated with this type of design (e.g., lack of appropriate control/comparison group) and the availability of a number of randomized trials.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

- Hotte S, Waldron T, Canil C, Winquist E, and members of the Genitourinary Cancer Disease Site Group. Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a clinical practice guideline. Available on the PEBC section of the CCO Web site at <http://www.cancercare.on.ca/>.
- Hotte S, Waldron T, Canil C, Winquist E, and members of the Genitourinary Cancer Disease Site Group. Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer: a systematic review. Available on the PEBC section of the CCO Web site at <http://www.cancercare.on.ca/>.

Funding

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Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline 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 responsibility for their application or use in any way.

Contact Information

For further information about this Evidence-based Series, please contact Dr. Himu Lukka, Chair, Genitourinary Cancer Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2; TEL (905) 387-9711 ext. 67699; FAX (905) 575-6326.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site 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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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;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol.* 1998;16(3):1226-31.

EBS 3-8-2 Document Assessment and Review Tool.



DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	3-8-2 Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer
Date of current version	8 June 2006
Clinical reviewer	Dr. S. Hotte Dr. Eric Winquist
Research coordinator	Rovena Tey
Date initiated	15 June 2010
Date and final results / outcomes	2 March 2011 ENDORSED
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document as is ? Answer Yes or No, and explain if necessary:	<div>1. YES</div> <ul style="list-style-type: none"> This document is needed by the University Health Network (UHN) and Ministry of health (MOH) to create an Ontario-based Interleukin-2 (IL2) treatment program. <div>If No, then the document should be ARCHIVED¹ with no further action; go to 11. If Yes, then go to 2.</div>
2. Are all the current recommendations based on the current questions definitive ^s or sufficient ^s , and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:	<div>2.</div> <ul style="list-style-type: none"> Definitive - NO; Sufficient - NO <ul style="list-style-type: none"> The existing guideline did not identify any trials that evaluated high-dose IL2 in comparison to a non-high-dose IL2 regimen <5 y elapsed - YES <div>If Yes, the document can be ENDORSED² with no further action; go to 11. If No, go to 3.</div>
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	<div>3. NO</div> <div>If Yes, the document should be taken off the Web site as soon as possible. A WARNING¹ should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.</div>
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	<div>4. YES</div> <ul style="list-style-type: none"> there is a designated research co-ordinator at the PEBC to carry out the literature search <div>If No, a DEFERRAL³ should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.</div>
5a. Guideline Research Questions. Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment and Review process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this form and answer NO).	

Changes to the research question:

- To address the needs of the UHN and MOH for creating an IL2 treatment program, this guideline needs to specifically relate to high-dose IL2
- Therefore, the research Q needs to be changed to specifically evaluate high-dose IL2
- To ensure that we can include more studies, we need to remove the comparison group from the research question

Question:

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

5b. Inclusion and Exclusion criteria. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

- Focus on high-dose IL2 studies
- Broaden inclusion criteria to include non-randomized phase 2 studies and remove the comparison group so that this guideline can include all studies of high-dose IL2

Inclusion criteria:

Articles were selected for inclusion in this systematic review if they were fully published reports or abstracts of **non-randomized phase 2 trials**, RCTs, or meta-analyses of RCTs ~~comparing~~ **evaluating single-agent high-dose IL-2 -containing treatment regimens to regimens without IL-2** in patients with unresectable or metastatic 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-RCC patients were eligible as long as the outcomes for RCC patients were analyzed separately. Existing systematic reviews or evidence-based practice guidelines relevant to the guideline question were also eligible.

Exclusion criteria:

~~RCTs~~ **Studies** that compared either surgery or radiotherapy with IL-2 immunotherapy were excluded. **Studies of IL-2 in combination with other therapies were also excluded.**

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):

Articles were selected for inclusion in this systematic review if they were fully published reports or abstracts of non-randomized phase 2 trials, RCTs, or meta-analyses of RCTs evaluating high-dose IL-2-containing treatment regimens in patients with unresectable or metastatic 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-RCC patients were eligible as long as the outcomes for RCC patients were analyzed separately. Existing systematic reviews or evidence-based practice guidelines relevant to the guideline question were also eligible.

Exclusion criteria:

Studies that compared either surgery or radiotherapy with IL-2 immunotherapy were excluded.

Search Period:

- 2005 to 13 July 2010 (Medline to week 27 + Embase to June week 4)
- 2005 to 2010 (ASCO Annual Meeting)
- 2005 to 2010 (American Urological Association)

Brief Summary/Discussion of New Evidence:

Of 924 total hits from Medline + Embase and looking through 517 abstracts from ASCO + 196 abstracts from the American Urological Association conference, 3 references representing 3 potentially new studies were found evaluating single-agent high-dose IL2 in metastatic or unresected renal cell carcinoma, of which 1 was a full text publication and 2 were abstracts.

Interventions	Study type	Population	Outcomes	Brief results	References
High-dose IL2	SELECT trial (Cytokine Working Group)	Metastatic or unresectable renal cell carcinoma	PFS, response rate, toxicity	<ul style="list-style-type: none">• Median PFS = 4.4 mo• Response rate = 29%• 2 treatment related deaths• No unanticipated toxicities	(McDermott DF et al. 2010) [abstract]
High-dose IL2 <u>vs.</u> low-dose IL2	Meta-analysis of 2 RCTs	Advanced renal cell cancer	1 = OS 2 = Remission	For high-dose vs. low-dose IL2 <ul style="list-style-type: none">• OS = Grps did not differ• Remission = OR 1.82 (1 to 3.3), favours high-dose IL2	(Coppin C et al. 2008)
high-dose IL-2 <u>vs.</u> IL-2 (after anti-VEGF)	Retrospective study vs. high-dose IL2 arm of ph 3 trial	Metastatic renal cell carcinoma, previously treated with anti-VEGF (bevacizumab, sorafenib, sunitinib)	Toxicity, partial or complete response	<ul style="list-style-type: none">• Toxicities of IL2 therapy after anti-VEGF therapy included hypotension, pulmonary edema, acute renal failure• Pts previously treated with sunitinib or sorafenib had higher incidence of severe cardiac toxicities than pts who received high-dose IL2 (50% vs. 8.5%)• No partial or complete responses were seen	(Schwarzberg T et al. 2008) [abstract]

DFS = disease-free survival; IL = interleukin; ph = phase; OS = overall survival; PFS = progression-free survival; pts = patients

New References Identified (alphabetic order):

Coppin C, Porzsolt F, Autenrieth M, et al. (2008) Immunotherapy for advanced renal cell cancer. Cochrane Database of Systematic Reviews(4).

McDermott DF, Ghebremichael MS, Signoretti S, et al. (2010) The high-dose aldesleukin (HD IL-2) "SELECT" trial in patients with metastatic renal cell carcinoma (mRCC). ASCO Meeting Abstracts 28(15 Suppl): 4514.

Schwarzberg T, Regan MM, Liu V, et al. (2008) Retrospective analysis of interleukin-2 therapy in patients with metastatic renal cell carcinoma who had received prior antiangiogenic therapy. ASCO Meeting Abstracts 26(15 Suppl): 5044.

Literature Search Strategy:

Medline

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy\$ or metaanaly\$).tw.
4. (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.
5. (systematic adj (review\$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (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.
9. (reference list\$ or bibliograph\$ or hand-search\$ or relevant journals or manual search\$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.

11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi\$ control\$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. 20 or 21
23. (clinic\$ adj trial\$1).tw.
24. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp carcinoma, renal cell/
39. exp kidney neoplasms/
40. (renal and (carcinoma or cancer or neoplasm or tumor?r)).tw.
41. (kidney and (carcinoma or cancer or neoplasm or tumor?r)).tw.
42. 38 or 39 or 40 or 41
43. (immunotherapy or interleukin or interleukins or interleukin-2 or interleukin 2 or IL2 or IL-2).tw.
44. interleukin-2/ or IL-2/
45. 43 or 44
46. 42 and 45
47. 37 and 46
48. (2005\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$).ed.
49. 47 and 48

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 syntheses? 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 psychlit 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. (clinic\$ adj trial\$1).tw.
18. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3 or dummy)).tw.
19. placebo/
20. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
21. (allocated adj2 random).tw.
22. or/17-21
23. practice guidelines/
24. practice guideline?.tw.
25. practice guideline.pt.
26. or/23-25
27. 9 or 10 or 11 or 15 or 16 or 22 or 26
28. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
29. 27 not 28
30. limit 29 to english

31. limit 30 to human
32. exp carcinoma, renal cell/
33. exp kidney neoplasms/
34. (renal and (carcinoma or cancer or neoplasm or tumor?r)).tw.
35. (kidney and (carcinoma or cancer or neoplasm or tumor?r)).tw.
36. 32 or 33 or 34 or 35
37. (immunotherapy or interleukin or interleukins or interleukin-2 or interleukin 2 or IL2 or IL-2).tw.
38. interleukin-2/ or IL-2/
39. 37 or 38
40. 36 and 39
41. 31 and 40
42. (200510\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$).ew.
43. 41 and 42

ASCO Annual Meeting - manually checked all abstracts in the section "Genitourinary Cancer: Kidney Cancer" (2005 to 2010)

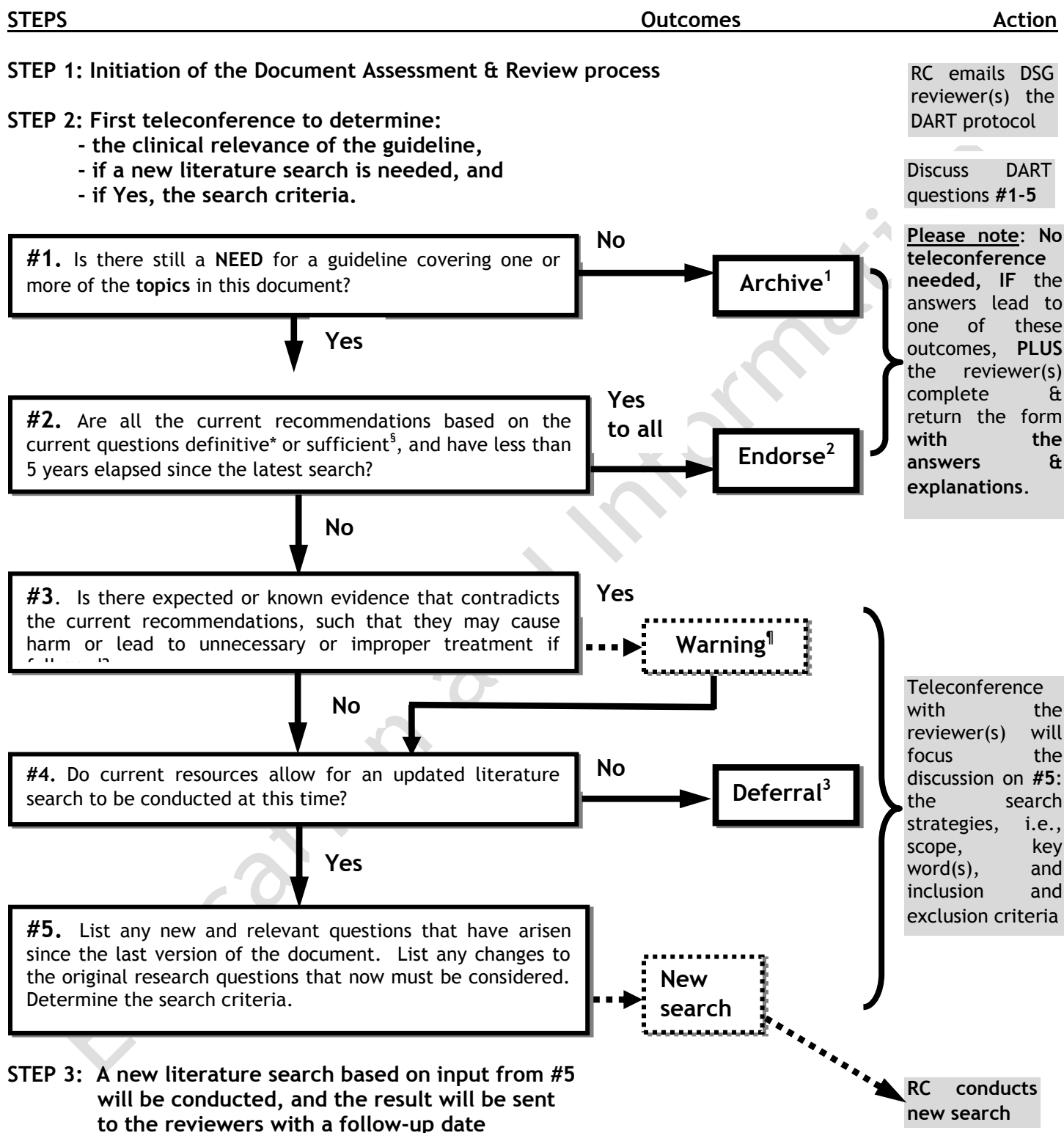
American Urological Association

- 2007 to 2010 - searched the Journal of Urology conference issue with keywords: interleukin [all fields]
- 2005 to 2006 - manually checked all abstracts in the section "Kidney & Ureteral Cancer: Evaluation & Treatment"

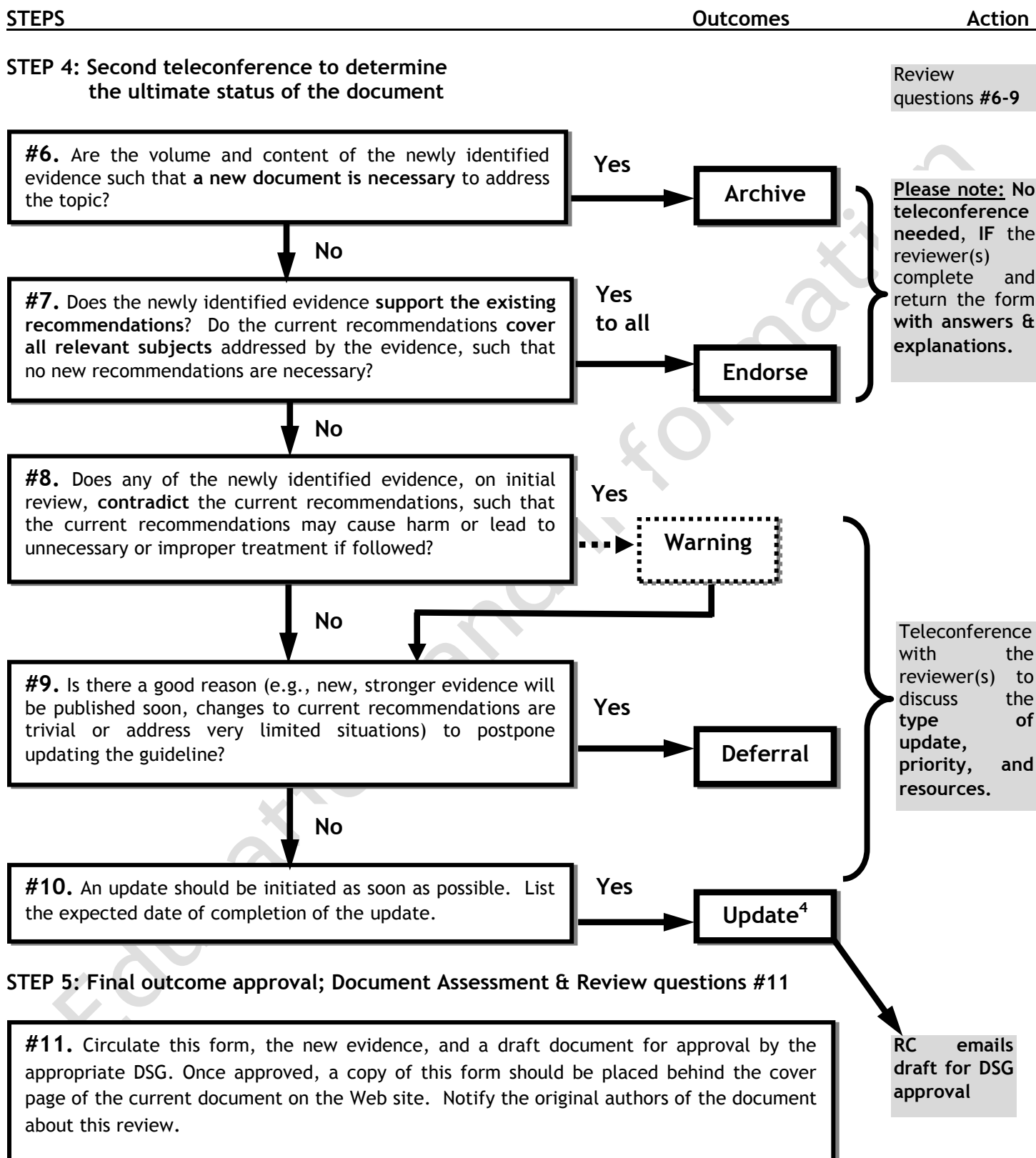
Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6. NO If Yes, then the document should be ARCHIVED with no further action; go to 11 . If No, go to 7 .
7. On initial review, does the newly identified evidence support the existing recommendations ? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	<ul style="list-style-type: none"> • The previous recommendations in the guideline are still valid • At this time, there is still a lack of evidence on high-dose IL-2 vs. placebo or vs. former or current standards of care • Therefore, Guideline 3-8-2 can be ENDORSED. If Yes, the document can be ENDORSED . If No, go to 8 .
8. 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:	8. Not applicable. If Yes, a WARNING note will be placed on the web site. If No, go to 9 .
9. 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:	9. Not applicable. If Yes, the document update will be DEFERRED , indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10 .
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. Not applicable. An UPDATE ⁴ will be posted on the Web site, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.	
DSG Approval Date:	2 March 2011
Comments from DSG members:	The new evidence did not change the recommendations.

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

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. **DEFERRAL** - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.
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.