Evidence-Based Series 3-8-1 EDUCATION AND INFORMATION 2012

Interferon-alfa in the Treatment of Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer

C. Canil, S. Hotte, L. A. Mayhew, T. Waldron, 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)

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods
and External Review Process

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

Interferon-alfa in the Treatment of Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Guideline Recommendations

C. Canil, S. Hotte, L. A. Mayhew, T. Waldron, 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)

Report Date: May 12, 2009

QUESTION

Is interferon-alfa (IFN-α) an effective treatment option for patients with inoperable locally advanced or metastatic renal cell cancer (RCC)? Specifically, does it improve overall or progression-free survival, tumour response rate, and/or quality of life? What are its adverse effects?

TARGET POPULATION

Adult patients with inoperable locally advanced or metastatic RCC.

RECOMMENDATIONS

- Results from recent randomized trials indicate that inhibitors of angiogenesis such as sunitinib and temsirolimus are of superior clinical effectiveness to IFN-α and therefore are recommended as preferred treatment options. (See Related Guidelines Evidence-based Series [EBS] #3-8-4)
- When angiogenesis inhibitors are not available or not recommended, single-agent IFN-α improves survival and disease control compared to older alternative therapies (such as IFN-gamma [IFN-γ] or medroxyprogesterone acetate) and represents a potentially effective alternative treatment option.
- The benefits of combined immunotherapy including IFN-α over IFN-α therapy alone are unclear, and this approach should not be routinely offered outside of clinical trials. (See Related Guidelines EBS #3-8-2)

QUALIFYING STATEMENTS

- The dose and duration of IFN-α varied across trials. The largest trial reporting benefit gave one dose of 5 MU subcutaneously followed by 10 MU subcutaneously on a thrice

weekly schedule for a total of 12 weeks until progressive disease discontinued or objective response continued longer.

- This guidance is issued as part of a series of articles on metastatic RCC and as such does not address issues covered by the other guidelines.
- For patients with metastatic disease treated with cytoreductive nephrectomy, IFN-α should be prescribed in accordance with the doses used in the clinical trials. (See Related Guidelines EBS #3-8-3)
- Both IFN-α-2a and IFN-α-2b appear to have similar efficacy and toxicity.
- The effectiveness of IFN-α varies between patients. Its choice as therapy should be made in consultation with a physician experienced in the use of IFN-α, as the side effects of treatment can be substantial and must be considered with respect to the patient's age and performance status.

KEY EVIDENCE

- Meta-analyses of randomized clinical trials (RCTs) comparing IFN-α-based therapy with control treatment demonstrated an improvement in overall survival (six RCTs [n=992]; hazard ratio=0.79; 95% confidence interval, 0.69-0.91) with IFN-α-based therapy. This is equivalent to a 21% reduction in the risk of death over the time course of the RCTs included in this analysis.
- In a large RCT comparing IFN-α alone to medroxyprogesterone, lack of appetite, tiredness, nausea and vomiting, lack of energy, dry mouth, shivering, and depressed mood were more common with IFN-α therapy.
- A Cochrane meta-analysis of four RCTs reported no difference with regards to efficacy between IFN-α2a and IFN-α2b.

RELATED GUIDELINES

PEBC Evidence-based Series:
- #3-8-2: *Interleukin-2 in the Treatment of Patients with Unresectable or Metastatic Renal Cell Cancer*.
- #3-8-3: *The Role of Cytoreductive Nephrectomy in the Management of Patients Treated with Immunotherapy for Metastatic Renal Cell Cancer*.
- #3-8-4: *The Use of Inhibitors of Angiogenesis in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer*.

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

Interferon-alfa in the Treatment of Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Evidentiary Base

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QUESTION

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INTRODUCTION

In 2009, approximately 4,600 new RCC cases and 1,600 RCC deaths were projected for Canada. Of these, approximately 1,600 new cases and 550 deaths would occur in Ontario (1). At the time of first diagnosis, 45% of patients would present with localized disease, 25% would have locally advanced disease with lymph node or local organ involvement, and the remaining 30% would present with metastases (2). While roughly 50% of patients presenting with localized disease are expected to live at least five years, patients with metastatic involvement have a five-year survival rate of less than 10%. The median survival time of these patients is less than 12 months but can be quite variable, depending on a number of prognostic factors that include performance status, levels of lactate dehydrogenase (LDH), hemoglobin, calcium, time to treatment, prior radiotherapy, and number of metastatic sites (3).

Patients who present with localized disease are best treated with surgery; however, as many as 30% of these patients will eventually relapse (4). When patients present with or develop inoperable locally advanced or metastatic disease, the main intent of treatment is to effectively control symptoms and provide a chance of improved survival. Unfortunately, the treatment of late-stage RCC remains a challenge to oncologists and urologists; unlike other

solid malignancies, advanced or metastatic RCC is highly resistant to most available chemotherapeutic agents (5,6).

Immunotherapy was first suggested as a treatment for advanced or metastatic RCC after occasional spontaneous tumour regressions, and the presence of anti-tumour immune responses were observed in patients with this neoplasm (7). The major immunological approaches that have been investigated in these patients have included cytokines, either as single agents or in combination with other cytokines or chemotherapy (8). One of the first classes of cytokines to be evaluated was interferon. Interferons are naturally occurring glycoproteins that are produced in response to viral infections, antigens, and mitogens and are often induced by other cytokines like tumour necrosis factor (TNF) and interleukins (9). The anti-tumour activity of interferons is mediated by various mechanisms, such as immunomodulation, antiproliferative activity, inhibition of angiogenesis, regulation of differentiation, interaction with growth factors, and modulation of gene expression (9). The present systematic review assesses the effectiveness of IFN-α for the treatment of advanced or metastatic RCC, based on the results of reported randomized controlled trials (RCTs).

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (10). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the PEBC Genitourinary Cancer Disease Site Group (GU DSG) and one methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on IFN-α for inoperable locally advanced or metastatic RCC. The body of evidence in this systematic review is primarily comprised of mature RCT data, and forms the basis of a clinical practice guideline developed by the GU DSG. This systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

MEDLINE (1966 through May 2009) and EMBASE (1980 through 2009 week 19) were searched for relevant papers. MEDLINE was searched using the following medical subject headings: "carcinoma, renal cell", "kidney neoplasms", "immunotherapy", "interferon-alfa", and "interferon"; EMBASE was searched using the following Excerpta Medica tree terms: "kidney tumor", "kidney cancer", "immunotherapy", and "interferon". In each database, those subject headings were combined with the following disease and treatment-specific text words: "renal cancer", "kidney cancer", "immunotherap:", "interferon", and "IFN". 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 (2009, Issue 2) and the meeting proceedings of the American Society of Clinical Oncology 1995-2008, the ASCO genitourinary symposia (2008-2009), and the American Urological Association (1995-2009) 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
Inclusion Criteria
Report Types
- Fully published RCTs, abstracts of RCTs, or meta-analyses that compared IFN-α-containing treatment regimens to regimens without IFN-α.

Study Types
- Randomized phase II and phase III studies.

Patient Characteristics
- Patients with inoperable locally advanced or metastatic RCC.
- RCTs including non-RCC patients were eligible as long as outcomes were analyzed separately for RCC patients.

Outcomes
- Reports were required to provide data on at least one of the following outcomes: response rate, survival (overall, progression-free, and time-to-progression), toxicity, and quality of life.

Controls
- Placebo.
- Cytotoxic chemotherapy was considered a potentially appropriate control therapy on the basis of lack of anti-tumour activity and patient benefit identified in clinical trials (11).
- Hormonal therapies such as medroxyprogesterone (MPA) were considered appropriate control therapies on similar grounds to chemotherapy.
- IFN-γ has been tested as a therapy for RCC but was considered as a control therapy equivalent to placebo for the purpose of this review. This assumption was considered justified by the results of a large RCT in RCC that reported no difference in objective response or survival when compared to placebo (12).

Exclusion Criteria
- RCTs that compared surgery or radiotherapy with IFN-α-containing treatment.
- RCTs that compared IFN-α with angiogenesis inhibitors were excluded as these comparisons are addressed in Evidence-based Series (EBS) #3-8-4.
- RCTs that compared IFN-α with interleukin-2 (IL-2) were excluded as these comparisons are addressed in EBS #3-8-2.

Synthesizing the Evidence
For some eligible trials, odds ratios (OR) for overall mortality at one year and objective response, and hazard ratios (HR) for overall mortality were available from a Cochrane meta-analysis by Coppin et al (13). The analytic plan was to combine published data on these endpoints for all eligible trials, using meta-analysis. When the HR and its associated variance were available, those statistics were either extracted directly from the trial itself, from the Cochrane meta-analysis (13), or were obtained through personal communication with trial authors. Otherwise, the HR was estimated indirectly from data extracted from published Kaplan-Meier curves (14-16), using the methods of Parmar et al

(17). If data were not provided from which HR could be derived, or the authors did not provide the HR, the trial was not included in the meta-analysis. To estimate the overall effect of IFN-α, the data were combined using Review Manager version 4.2 (18). Results are expressed as HR or OR with 95% confidence intervals (CI), where values <1.0 represent a benefit for IFN-α over the alternative (for HR and OR of mortality), and values >1.0 indicate a benefit for IFN-α (for OR of response). Use of a random effects model was planned.

RESULTS
Literature Search Results
Ninety-eight unique RCTs of IFN-α were identified by the literature search, and eight of those met the eligibility criteria (14-16,19-26). The search also located two systematic reviews with meta-analyses (13,27). No evidence-based guidelines were identified.

Systematic Reviews with Meta-analyses
In 2001, Coppin et al reported results of a Cochrane systematic review and meta-analysis. An update of this review was published in 2005 (13). A third meta-analysis published in 1999 (27) is not discussed here as the Cochrane review includes more recent data.

To answer our guideline question "Is IFN-α an effective treatment option for patients with inoperable locally advanced or metastatic RCC?" the most relevant comparison from the Cochrane meta-analysis was "Comparison 05: IFN-α vs. non-IFN-α control" (See Table 1). The pooled results of four RCTs showed that IFN-α was associated with reduced one-year mortality and greater remission rates when compared to controls (MPA or vinblastine [VBL]). Remission was defined as the number of patients receiving a partial or complete response. The pooled remission rate was 12.5% for IFN-α versus 1.5% for controls, with a pooled OR of 7.61 (95% CI, 3.02-19.2). IFN-α was also associated with reduced one-year mortality (OR=0.56; 95% CI, 0.40-0.77).

The four trials in comparison 05 were also pooled using the methods of Parmar et al (17) in order to further explore the impact of IFN-α on mortality outcomes. The estimated HR for each of the four trials were as follows: Hancock et al (22,23) HR=0.74 (95% CI, 0.60-0.92); Pyrhönen et al (25) HR=0.65 (95% CI, 0.47-0.91); Kriegmair et al (24) HR=0.67 (95% CI, 0.37-1.22); and Steineck et al (26) HR=1.05 (95% CI, 0.64-1.72). The pooled overall HR for death was 0.74 (95% CI, 0.63-0.88), indicating a survival benefit for IFN-α over controls. The authors concluded that IFN-α demonstrated a modest improvement in remission rates and a consistent and statistically significant mortality reduction compared to a variety of controls. The analysis that compared trials using the recombinant subtypes IFN-α-2a and IFN-α-2b showed no evidence of statistical heterogeneity for either objective response or one-year mortality.

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 05: IFN-α vs. Non- IFN-α Control			
Mortality at 1 year	Kriegmair 1995, (24) Hancock 2000, (22,23) Pyrhönen 1999, (25) Steineck 1990, (26)	14/35 vs. 20/28 95/167 vs. 114/168 35/79 vs. 48/78 21/30 vs. 22/30	0.56 (0.40, 0.77) p=0.0005
Remission[1]	Kriegmair 1995, (24) Hancock 2000, (22,23) Pyrhönen 1999, (25) Steineck 1990, (26)	9/44 vs. 0/45 16/167 vs. 2/168 13/79 vs. 2/81 2/30 vs. 1/30	7.61 (3.02, 19.18) p=0.00002

[1]Remission is defined as the number of patients receiving a partial or complete response.

Randomized Controlled Trials
Trial Characteristics

Eight RCTs comparing IFN-α either alone or plus control therapy to control therapy alone published between 1988 and 2009 form the basis of this systematic review (14-16,19-26).

A total of 1,360 eligible patients were randomized across the trials, with patient accrual per trial arm ranging from 16 to 176. Patients were eligible for inclusion if they had histologically confirmed RCC and showed no signs of brain metastases. The median age of patients ranged from ≤55 to 63 years, and the majority of patients were male (range, 59 to 75%) with good performance status (i.e., Eastern Cooperative Oncology Group [ECOG] or World Health Organization [WHO] <2, Karnofsky >80% or Zubrod <2). The eight RCTs provided a total of 15 comparisons (one four-arm trial, one three-arm trial, and six two-arm trials). Regimen and dose details from these trials are summarized in Table 2.

Trial Quality

Based on their reports, the quality of the trials was generally suboptimal. There were inconsistencies in data reporting in several of the trials. Two studies did not report the number of patients randomized per arm (19,20). In addition, there were inconsistencies within a report regarding the number of patients reported, treated, and randomized (14-16,20,22,23); in some cases, different publications of the same trial reported a different number of patients randomized. Some of these issues were resolved through personal correspondence either with the study authors or with the author of the Cochrane review. However, the new data provided often conflicted with the data presented in the original papers. In addition, one study reported two responses in the combination arm of the trial and one in each of the other arms but did not report the type of response (21). Two studies did not report mortality data (19,21). Study quality elements of the included trials are summarized in Table 3.

Table 2: Trial Descriptions and Outcomes: IFN-α containing regimens vs. control (8 RCTs, 8 comparisons).

Trial	Treatment Arms	Route, Dose, and Schedule	No. Patients randomized (evaluable)	Objective Response Rate %				Survival				Progression-free Survival	
				OR	CR	PR	p-value[1]	Median (mos)	p-value[1]	1-yr %	5-yr %	Median (mos)	p-value[1]
Negrier 2005/6[2] (14-16)	IFN	sc 9 MU tiw	122 (115)	4.4[3] 8.7[4]	0.9[3] 0.4[4]	3.5[3] 2.5[4]	NR	15.2 (range 12.8-19.9)	NS	62.7[5]	NR	3.4	NR
	MPA	po 200 mg/d	123 (120)	2.5[3] 1.6[4]	0.8[3] 1.3[4]	1.7[3] 6.6[4]		14.9 (range 11.7-19.2)		59.5[5]		3.0	
Dutcher, 2003 (20)	IFN-γ + IFN-α	iv 0.3 mg/m^2 daily x5d repeated q 3w sc 10 MU/m^2 daily	NR (49)	10	4	6	NR	10.9	NR	47[5]	NR	FFS 2.9	NR
	IFN-γ	sc 0.1 mg/m^2/wk x 6 wks	NR (39)	0	0	0		7.0		39[5]	NR	FFS 1.4	
Hancock, 2003 (22,23)	IFN-α	sc 10 MU tiw x 12 wks	174 (167)	14[6]	NR	NR	0.001	9.0	0.013	43	NR	4	NR
	MPA	po 300 mg q d x 12 wks	176 (168)	1[6]	NR	NR		6.8		32	NR	3	
Pyrhönen, 1999 (25)	IFN-α2a + VBL	sc or im 3 MU tiw for 1wk, then sc 18 MU tiw[7] iv 0.1 mg/kg q 3 wks	79 (79)	16.5	8.9	7.6	0.0025	15.5	0.0049	55.7	4.1	3	0.0001
	VBL	iv 0.1 mg/kg q 3 wks	81 (81)	2.5	1.2	1.2		8.7		38.3	0	2	
Kriegmair, 1995 (24)	IFN-α + VBL	sc 8 MU tiw[8] iv 0.1 mg/kg q 3 wks	44 (41)	20	9	11	0.001	NR	NS	60[5]	NR	NR	NR
	MPA	im 500 mg/wk	45 (35)	0	0	0		NR		30[5]	NR	NR	
Steineck, 1990 (26)	IFN-α2a	im 10 MU/m^2 tiw[9] dose was escalated wkly by 2.5 MU/m^2 to a max of 20 MU/m^2	30 (NR)	6	3	3	NR	NR	NR	30[5]	NR	NR	NR
	MPA	im 1g tiw x 5 wks; 1g once a week	30 (NR)	3	3	0		NR		26[5]	NR	NR	
Dexeus, 1989 (19)	IFN-α	im 3 MU/m^2 d1, 15; 5 MU/m^2 d 2,16; 10 MU/m^2 d, 3-5,17-19[10]	NR (16)	12	0	12	NR	8.8	NR	NR	NR	NR	NR
	5-FU+ CIS + DOX+ MMC (FAMP)	iv 750mg/m^2 d 1-5 iv 75 mg/m^2 d 1[11] iv 25mg/m^2 d 2,3 iv 5 mg/m^2 d 4,5 , Cycle repeated every 28 days.	NR (16)	12	6	6		9.1					
Foon 1988 (21)	IFN-α	sc 2 MU/m^2 tiw	21(21)										

| IFN-γ | sc 1 MU/m^2 tiw0 | 21(21) | 2 PR 2 CR[13] | NR | NR | NR | NR | NR | NR | NR |
| IFN-α + IFN-γ [12] | | 47(47) | | | | | | | | |

Abbreviations: 5-FU = 5-fluorouracil; DOX = doxorubicin; bid = twice daily; CIS = cisplatin; CR = complete response; d = day; h = hour; IFN-α = interferon-alfa; IFN-γ = interferon-gamma; IL-2 = interleukin-2; im = intramuscularly; IU = International Units; iv = intravenous; kg = kilogram; m = metres; mg = milligrams; MMC = mitomycin C; MPA = medroxyprogesterone acetate; mos =-months; MU = Million Units; NR= not reported; NS = non-significant; OR = objective response; po = per oral; pts. = patients; PR = partial response; q = every; sc = subcutaneous; tiw = three times a week; VBL = vinblastine; vs. = versus; wk(s) = week(s); yr = year; µg = microgram.

[1] Only statistically significant differences are presented.
[2] This trial had two other arms which are not reported here as they are not included in the meta-analysis.
[3] At three months
[4] At six months
[5] Data extracted from survival curve.
[6] Overall response rate is based on 153 patients and 156 patients in the IFN-α and MPA treatment groups at 12 weeks, respectively. The overall response rate at six months for the IFN-α and MPA was 8% and 1%, p=<0.001, respectively.
[7] For patients unable to tolerate IFN-α treatment at a dose of 18 MU m^2, the dose was reduced to 9 MU m^2.
[8] on three consecutive days
[9] First 10 patients received an initial dose of 50 MU/ m^2 tiw, however the dose was lowered due extensive side effects.
[10] 10 people received purified, 6 received recombinant IFN-α.
[11] or 50mg/m^2 if creatinine clearance rate was between 40 and 50ml/min or 75mg/m^2 if creatinine clearance was greater than 50ml/min.
[12] While this arm of the trial was not used in the meta-analyses, all three arms have been included here as data on responses was not broken down by trial arm.
[13] Two responses occurred in the combination arm and one in each of the IFN-α and IFN-γ arms, type of response not specified.

Table 3: Quality of eligible trials.

Trial	Description of random allocation	Design	Non-inferiority margin	Power	Planned sample size	Sample size met?	Intention-to-treat analysis	Per protocol analysis?	Details of withdrawals and exclusions	Blinding
Negrier 2005/2006 (14-16)	No	2x2 factorial	10%	80%, 5% α error ß=20%	456	Yes	Yes	Yes	No	NA
Dutcher 2003 (20)	No	Randomized phase II 2-stage design for each arm	NA	NR	NR	NR	NR	NR	No	NA
Hancock 2003 (22,23)	Yes	Multicentre randomized trial Group-sequential analysis with triangular design.	12%	90% 5% significance	Maximum sample size 600	350 recruited[1]	Yes	NR	No	NA
Pyrhönen 1999 (25)	No	Phase III 2 arm	NA	80% One sided Two sided analyses used	160	Yes	Yes	No	NA	NA
Kriegmair 1995 (24)	No	2 arm	NA	NR	NR	NR	NR	NR	Exclusions yes Withdrawals no	NA
Steineck 1990 (26)	No	2 arm	NA	NR	NR	NR	No	Unclear	NR	NR
Dexeus 1989 (19)	No	2 arm	30%	Power 0.7 Significance 0.1	32	Yes	NR	NR	NR	NA
Foon 1988 (21)	Yes	3 arm	NA	NR	NR	NR	NR	NR	NR	NR

Abbreviations: NA – not applicable; NR – not reported
[1] Trial stopped early on advice of independent data monitoring committee.

Outcomes
Objective Response Rate

Tumour response data as reported in the randomized trials of IFN-α can be found in Table 2. Three of the randomized trials reported statistically significant response rates favouring IFN-α (22-25). Hancock et al (22,23) reported overall response rates for IFN-α and MPA as 14% and 1%, (p=0.001), respectively. Pyrhönen et al (25) and Kriegmair et al (24) compared combinations of IFN-α and vinblastine (VBL) to VBL alone and to MPA, respectively. The statistically significant objective response rates in the two trials were reported as 16.5% and 20% for the IFN-α combination and 2.5% and 0% for VBL and MPA, respectively.

Survival

Survival data for patients in the randomized trials of IFN-α can be found in Table 2. Median survival data were reported in five trials and ranged from 8.7 to 15.5 months for IFN-α-containing regimens and 6.8 to 14.9 months for non-IFN-α regimens. Two of the five trials reported statistically significant differences in overall survival favouring the IFN-α treatment arms (22,23,25). Hancock et al (22,23) randomized patients to either IFN-α or MPA treatment and observed an increased median survival for patients in the IFN-α arm (nine versus 6.75 months, p=0.013). Pyrhönen et al (25) reported that patients receiving IFN-α2a combined with VBL demonstrated a median survival of 15.5 months, while patients receiving VBL alone showed a median survival of 8.7 months (p=0.0049). Of the remaining three trials, one found no difference between trial arms (14-16), and two did not provide statistical comparisons (19,20). A sixth trial reported no difference in median survival between trial arms; however, no data were reported (24). One-year survival data were reported in two trials (22,23,25) and extracted from survival curves in four trials (14-16,20,24,26) (Table 2). Two trials did not report survival data (19,21).

Disease Progression

Disease progression was assessed in three trials (20,22,23,25), with details available in Table 2. The trial by Pyrhönen et al (25) reported that IFN-α2a in combination with VBL demonstrated significantly longer progression-free survival than did treatment with VBL alone (three versus 2.1 months, p=0.0001).

Toxicity

The adverse effects of IFN-α are well known and reasonably consistent from trial to trial, although these increase in intensity and frequency with increased IFN-α dose. Therefore, we have selected the toxicities reported from a large randomized trial as representative of IFN-α toxicity. Hancock et al (22,23) reported increased rates of lack of appetite (51%), tiredness (68%), nausea/vomiting (26%/9%), lack of energy (65%), dry mouth (41%), shivering (23%), and depressed mood (25%) with IFN-α after four weeks of treatment. Increased rates of lack of appetite, tiredness, lack of energy, dry mouth, and shivering persisted at 12 weeks. Other reported symptoms included irritability, worrying, sore muscles, general pain, nervousness, despondent or tense feelings, difficulty in sleeping, headaches, dizziness, decreased sexual interest, restlessness, anxiety, constipation, diarrhea, tingling in hands and feet, difficulty in concentrating, sore mouth, loss of hair, shortness of breath, hoarseness, and burning eyes.

Quality of Life

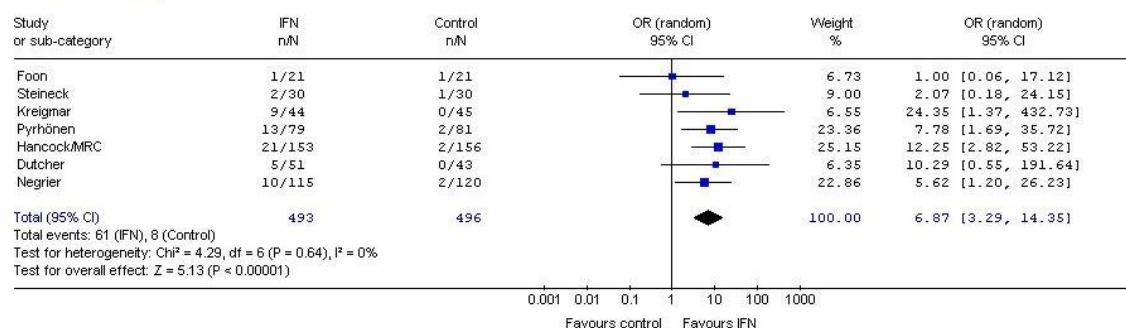No RCTs formally assessed health-related quality of life.

Meta-analysis

Overall response and mortality were considered the primary endpoints for meta-analysis. Owing to the previously mentioned issues with data consistency, study authors and the author of the Cochrane review were contacted for clarification. Responses from authors sometimes provided data that were different from that reported in the trial papers. For the purposes of this meta-analysis, responses from the authors were used as opposed to the data reported in trial reports. For the trial by Hancock et al (22,23), the number of patients that had reached 12 weeks of follow-up at time of analysis was used, since the response data reported in the paper were based on this number of patients (and not the full number of patients in the study). For the patients in the Negrier et al trial (14-16), the number of patients reported in the ASCO presentation was used, since this was the data used to calculate the HR for the meta-analysis, and these numbers matched those given in personal correspondence. Some additional data were also obtained through personal correspondence. For the patients reported in the Dutcher et al trial (20), the number obtained from personal correspondence was used. For the papers by Pyrhönen et al (25), Kreigmair et al (24), and Steineck et al (26), the data reported in the Coppin et al Cochrane review (13) and confirmed by the author of this report was used. For the paper by Foon et al (21), the data used were derived from the original trial paper.

Response

The response data from seven trials were pooled in a meta-analysis (14-16,20-26). As the number of patients randomized to each treatment arm was not available for one trial (19); this trial was not included in the meta-analysis. The results of the meta-analysis appear in Figure 1. The meta-analysis of the seven trials produced an OR of 6.87 (95% CI, 3.29-14.35; p<0.00001).

Figure 1: Meta-analysis of response in randomized trials of IFN-α vs. control in patients with inoperable renal cell cancer.
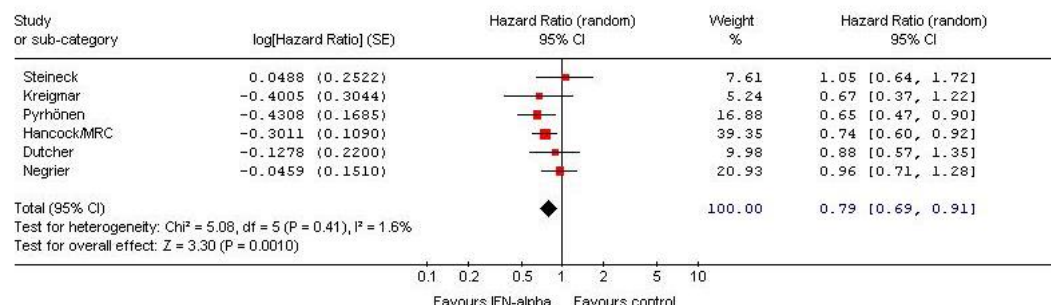
Study or sub-category	IFN n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Foon	1/21	1/21		6.73	1.00 [0.06, 17.12]
Steineck	2/30	1/30		9.00	2.07 [0.18, 24.15]
Kreigmar	9/44	0/45		6.55	24.35 [1.37, 432.73]
Pyrhönen	13/79	2/81		23.36	7.78 [1.69, 35.72]
Hancock/MRC	21/153	2/156		25.15	12.25 [2.82, 53.22]
Dutcher	5/51	0/43		6.35	10.29 [0.55, 191.64]
Negrier	10/115	2/120		22.86	5.62 [1.20, 26.23]
Total (95% CI)	493	496		100.00	6.87 [3.29, 14.35]

Total events: 61 (IFN), 8 (Control)
Test for heterogeneity: Chi² = 4.29, df = 6 (P = 0.64), I² = 0%
Test for overall effect: Z = 5.13 (P < 0.00001)

0.001 0.01 0.1 1 10 100 1000
Favours control   Favours IFN

Abbreviations: vs. = versus.

Meta-analysis of Mortality

Mortality data suitable for meta-analysis were reported in six trials and combined in a meta-analysis (14,20,22-26,28). The results of the meta-analysis appear in Figure 2. The HR for mortality after treatment with IFN-α was 0.79 (95% CI, 0.69-0.91; p=0.001).

Figure 2: Meta-analysis of mortality in randomized trials of IFN-α versus control in patients with inoperable renal cell cancer.

Study or sub-category	log[Hazard Ratio] (SE)	Hazard Ratio (random) 95% CI	Weight %	Hazard Ratio (random) 95% CI
Steineck	0.0488 (0.2522)		7.61	1.05 [0.64, 1.72]
Kreigmar	-0.4005 (0.3044)		5.24	0.67 [0.37, 1.22]
Pyrhönen	-0.4308 (0.1685)		16.88	0.65 [0.47, 0.90]
Hancock/MRC	-0.3011 (0.1090)		39.35	0.74 [0.60, 0.92]
Dutcher	-0.1278 (0.2200)		9.98	0.88 [0.57, 1.35]
Negrier	-0.0459 (0.1510)		20.93	0.96 [0.71, 1.28]
Total (95% CI)			100.00	0.79 [0.69, 0.91]

Test for heterogeneity: Chi² = 5.08, df = 5 (P = 0.41), I² = 1.6%
Test for overall effect: Z = 3.30 (P = 0.0010)

0.1 0.2 0.5 1 2 5 10
Favours IFN-alpha   Favours control

DISCUSSION

This review identified eight RCTs that directly evaluated the use of IFN-α in locally advanced or metastatic RCC. These trials compared IFN-α alone or in combination with other agents against control therapies considered to have little or no activity in RCC. In our meta-analysis of six trials, the overall HR for death was 0.79, indicating a 21% reduction in the risk of death for patients treated with IFN-α over the time periods of follow-up of the RCTs. Toxicity was higher with IFN-α therapy, and unfortunately, health-related quality of life was not evaluated. However, the odds of objective response were almost seven times higher for patients receiving IFN-α-containing regimens (4.4-20%) compared to patients in control groups (0-3%). Heterogeneity was minimal in these analyses. None of the included RCTs used placebo control arms, which is an inherent limitation of this data set. This could potentially exaggerate survival differences between IFN-α and control, because of the detrimental effects of control therapy, a development was more likely to occur when chemotherapy was the control. MPA and IFN-γ have not shown detrimental effects on survival, and analysis of these trials alone shows similar pooled survival results (data not shown). Only one trial included in the analyses used chemotherapy (single-agent VBL) as control (25). This trial did have the most extreme HR for overall mortality, favouring IFN-α therapy. However, VBL has a low objective response rate in RCC (7%) (11), is considered a mild cytotoxic drug, and was also included in combination with IFN-α in the experimental arm of this trial. A sensitivity analysis excluding the trial provided an overall HR for death of 0.83 (95% CI, 0.71-0.96, p=0.01). The limitations of published data meta-analysis have been well described and are potentially applicable to these results (29); nevertheless, we consider the results a comprehensive and robust synthesis of the best currently available clinical data.

Overall, toxicity appeared worse with IFN-α compared to non-IFN-α therapy. Toxicity for IFN-α is well known and consistent from trial to trial therefore we presented toxicity data from a large randomized trial (22,23) that reported increased rates of lack of appetite, tiredness, lack of energy, dry mouth, and shivering with IFN-α after 12 weeks of treatment. No toxic deaths were reported; however, these data were not reported in the majority of studies. The general opinion is that IFN-α regimens are associated with significant toxicity, and the magnitude of this toxicity may be underestimated in clinical trials due to patient selection factors such as performance status and under-reporting.

Doses and modality of administration of IFN-α differed across the trials. In five trials, IFN-α was administered subcutaneously at doses ranging from 2 MU/m^2 to 10 MU/m^2 on a thrice-weekly schedule (14-16,20-24). In two trials, IFN-α was administered intramuscularly at doses ranging from 3 MU/m^2 to 10 MU/m^2 (19,26), and in another it was administered either subcutaneously or intramuscularly starting at 3 MU and increasing to 18 MU (25). Whether there is a dose response to IFN-α is unclear; however, it is likely that toxicity is dependent on

dose and schedule. In addition, there is no evidence of a difference in efficacy between recombinant IFN-α2a and IFN-α2b, or clear evidence of benefit of adding chemotherapy to IFN-α. In view of this, the consensus of the authors was that it is reasonable to use the dose and schedule from the largest RCT showing benefit (22,23). This trial gave an initial dose of 5 MU subcutaneously followed by 10 MU subcutaneously on a thrice-weekly schedule for a total of 12 weeks unless progressive disease or objective response were seen. Treatment could be continued after 12 weeks in responding patients. In view of these data and the toxicities of IFN-α, the value of treatment beyond 12 weeks in non-responding patients is questionable and should be considered on an individual basis.

Despite many years of research, the prognosis for patients with inoperable locally advanced, or metastatic RCC had not changed until recently, and very few therapeutic options existed for these patients. Our synthesis of the data from randomized trials of IFN-α-based immunotherapy confirms that IFN-α has anti-tumour activity in RCC, provides a genuine if modest survival benefit in this patient population, and should be considered as a potential treatment option. Evidence from randomized trials of angiogenesis inhibitors (i.e., sunitinib, sorafenib, and temsirolimus) show that these agents are of superior clinical effectiveness to IFN-α, with acceptable toxicity. The clinical benefits observed with these agents make them the preferred treatment modality. In particular, the low objective response rate (ORR) seen with IFN-α (6-20%) suggests that drugs such as sunitinib (ORR=33-40%) may be preferred in patients with disease involving critical organs where prompt disease shrinkage to secure survival may be necessary. This topic is beyond the scope of this report and is addressed separately in EBS #3-8-4. Randomized trials of cytoreductive nephrectomy followed by IFN-α therapy have also shown modest survival benefits in this patient population. IL-2-based immunotherapy has not been shown to be superior to IFN-α in RCTs and is associated with greater toxicity. These topics are also beyond the scope of this report and are addressed separately in EBS #3-8-2 and #3-8-3.

As not all patients may have access to the newer angiogenesis therapies due to their costs, information about the effectiveness of IFN-α is still of value. Despite IFN-α and recent advances with other new drugs, patients with inoperable locally advanced or metastatic RCC continue to have an incurable malignancy, and further research to improve disease control and cure is necessary.

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, and none were identified.

CONCLUSIONS
Until recently, very few systemic therapeutic options existed for patients with inoperable locally advanced or metastatic RCC. Immunotherapy with IFN-α can be considered as a treatment option to modestly improve survival and disease control in this patient population. However, given the toxicity profile of IFN-α, patient factors such as age and performance status must be taken into consideration and may affect patients' ability to tolerate and benefit from therapy. Further, angiogenesis inhibitors have expanded the treatment repertoire for RCC and appear to have superior effectiveness compared to IFN-α. In view of this, the role of IFN-α in the treatment of RCC is less clear. However, as not all patients may have access to the newer therapies due to their costs, information about the effectiveness of IFN-α is still of value.

Locally advanced or metastatic RCC remains an incurable disease, current treatments remain palliative, and further research is warranted. Whenever possible, patients should be encouraged to participate in clinical trials.

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

Interferon-alfa in the Treatment of Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: EBS Development Methods and External Review Process

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

Report Date: May 12, 2009

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, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series
Each EBS is comprised of three sections:

- *Section 1: Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the guideline development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This EBS was developed by the Genitourinary Cancer Disease Site Group (GU DSG) of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on interferon-alfa (IFN-α) for the treatment of inoperable locally advanced or metastatic renal cell cancer (RCC), developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel
Prior to the submission of this EBS draft 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 Report Approval Panel included:
1. The DSG has completed EBS #3-8-4, which demonstrates superior outcomes with other treatment options (i.e., sunitinib and temsirolimus) directly or indirectly compared to IFN-α. The current EBS does not adequately account for an overall approach to treating RCC.
2. The DSG should indicate why response (as opposed to other endpoints) is used as a policy determining outcome measure for considering IFN-α treatment, especially since the toxicities associated with IFN-α are substantial.
3. It is not clear from the guideline question what IFN-α is being compared to (e.g., placebo, standard of care). Are the comparisons in the trials (i.e., vinblastine or medroxyprogesterone) the agreed-upon standard? This does not seem to be the case from what appears in the Discussion: "A potential limitation of these data is that none of the RCTs included used a placebo control arm. This could exaggerate survival differences between IFN-α and control arms due to detrimental effects of control therapy...this is more likely when chemotherapy is the control. The only included study with a chemotherapy control did have the most extreme point estimate favouring IFN-α therapy (3)." It is unclear how the explanation given by the DSG alleviates this concern. In addition, where is the evidence to support the statement that MPA and IFN-y have not shown detrimental effects on survival?
4. Further to (3) above, the trial by Dutcher et al (4) is treating IFN-y as a control because a large trial (5) found no difference between IFN-γ compared to placebo in MRCC. Is there a systematic review to back this up? If this comparison is only based on the one large trial, was the trial designed to be an equivalency trial? If not, the

Dutcher et trial should not be used in this way—it is answering a different question. The same issue applies to the Foon et al trial (6).

5. The data presented in Table 2 do not correspond with the numbers used in the meta-analysis. This includes both the numerator and the denominator. There is inconsistency in terms of which patients are included in the analysis; sometimes the number of randomized patients is used, and other times it is the number of evaluable patients. What was the time period of analysis, and was this consistent across the included trials?

6. Now that other treatment options have become available, the observation that INF-α has 'activity' is not sufficient to recommend its use. The relevance and currency of the guideline is not sufficiently stated. If IFN-α still has a role, it should be framed as being for patients who for medical reasons cannot receive the other therapies.

GU DSG Response

1. The GU DSG plans to develop an overarching guidance document addressing the treatment of RCC; however, the DSG believed that individual guidance for the different treatment approaches was warranted. As such, this guideline does rely heavily on the other guidelines in this series, particularly the guideline on inhibitors of angiogenesis.

2. Ideally, overall survival and quality of life are the optimal outcomes of interest. Unfortunately, quality of life data were not available, and data on disease control were also limited. Response can potentially be a measure of patient benefit; however, its value as a surrogate for patient benefit in RCC is limited. That being said, it is the outcome most frequently reported by the RCTs. To avoid the perception that this outcome is driving the recommendations, reference to response data has been removed from Section 1 of the report.

3. The rationale for allowing chemotherapy as control therapy is based on numerous studies evaluating a variety of chemotherapeutic agents that show a lack of significant activity or benefit of chemotherapy in RCC. The comparators used in this review are the same as those used in a recent Cochrane systematic review by Coppin et al (7). Motzer and Vogelzang (8) and Hartmann and Bokemeyer (5) also provide thorough reviews of this issue. Indeed, one author (9) has made a case for supportive care alone as the standard of care for advanced RCC, owing to the lack of efficacious treatments. To assess the robustness of the meta-analysis results, a sensitivity analysis was performed with the one chemotherapy control trial removed. The overall result of the meta-analysis of mortality data remained the same (HR=0.83; 95% CI, 0.71-0.96; p=0.01). The DSG added more explanation and the results of the sensitivity analysis to the Discussion in Section 2 of the report.

4. Although technically not designed as an equivalence trial, most clinicians accept this trial as demonstrating equivalence of IFN-γ to placebo. It certainly does not appear detrimental compared to placebo. To verify this point, the DSG completed a sensitivity analysis in which the Dutcher trial (4) was removed from the meta-analysis of mortality data. The overall result of the meta-analysis of mortality data remained the same (HR=0.79; 95% CI, 0.67-0.93; p=0.004).

5. Across the trials, the quality of reporting was consistently poor, and at times, there were conflicting reports within a paper as to the number of patients. As a result, for the meta-analyses, we contacted study authors and the author of the Cochrane review for clarification. At times, the data returned from this correspondence were different from what appears in the trial reports. The issues encountered with the data quality

and inconsistency and the details as to where the data was obtained for each trial are now documented more clearly in the report.

6. Sunitinib and temsirolimus are of superior clinical effectiveness to IFN-α and therefore are recommended as preferred treatment options. In many cases, owing to funding restrictions, treatment with IFN-α is the only option available to patients. The wording of the recommendations has been modified to reflect these issues.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the GU DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GU DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review February 25, 2009)
QUESTION

Is interferon-alfa (IFN-α) an effective treatment option for patients with inoperable locally advanced or metastatic renal cell cancer (RCC)? Specifically, does it improve overall or progression-free survival, tumour response rate, and/or quality of life? What are its adverse effects?

TARGET POPULATION

Adult patients with inoperable locally advanced or metastatic RCC.

RECOMMENDATIONS
- Results from recent randomized trials indicate that inhibitors of angiogenesis such as sunitinib and temsirolimus are of superior clinical effectiveness to IFN-α and therefore are recommended as preferred treatment options. (See Related Guidelines Evidence-based Series [EBS] #3-8-4)
- When angiogenesis inhibitors are not available or not recommended, single-agent IFN-α improves survival and disease control compared to older alternative therapies (such as IFN-gamma [IFN-γ] or medroxyprogesterone acetate) and represents a potentially effective alternative treatment option.
- The benefits of combined immunotherapy including IFN-α over IFN-α therapy alone are unclear, and this approach should not be routinely offered outside of clinical trials. (See Related Guidelines EBS #3-8-2)

QUALIFYING STATEMENTS
- The dose and duration of IFN-α varied across trials. The largest trial reporting benefit gave one dose of 5 MU subcutaneously followed by 10 MU subcutaneously on a thrice weekly schedule for a total of 12 weeks until progressive disease discontinued or objective response continued longer.
- This guidance is issued as part of a series of articles on metastatic RCC and as such does not address issues covered by the other guidelines.
- For patients with metastatic disease treated with cytoreductive nephrectomy, IFN-α should be prescribed in accordance with the doses used in the clinical trials. (See Related Guidelines EBS #3-8-3)
- Both IFN-α-2a and IFN-α-2b appear to have similar efficacy and toxicity.
- The effectiveness of IFN-α varies between patients. Its choice as therapy should be made in consultation with a physician experienced in the use of IFN-α, as the side effects of treatment can be substantial and must be considered with respect to the patient's age and performance status.

Methods

Targeted Peer Review: During the guideline development process, four targeted peer reviewers from Ontario, Quebec, and British Columbia considered clinical and/or methodological experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire 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 guideline. Written comments were invited. The questionnaire and draft document were sent out on February 25, 2009.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of genitourinary cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on March 15, 2009. The consultation period ended on April 15, 2009. The lead author reviewed the results of the survey.

Results

Targeted Peer Review: One response was received from two reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.** *(Consider: The appropriate stakeholders were involved in the development of the guideline. The evidentiary base was developed systematically. Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.)*					1
2. **Rate the guideline presentation.** *(Consider: The guideline is well organized. The recommendations were easy to find.)*				1	
3. **Rate the guideline recommendations.** *(Consider: The recommendations are clinically sound. The recommendations are appropriate for the intended patients.)*				1	
4. **Rate the completeness of reporting.** *(Consider: The guideline development process was transparent and reproducible. How complete was the information to inform decision making?)*				1	
5. **Does this document provide sufficient information to inform your decisions? If not, what areas are missing?**					1
6. **What are the barriers or enablers to the implementation of this guideline report?** Responses are compiled in the comments section below.					
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
7. **Rate the overall quality of the guideline report.**					1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
8. **I would make use of this guideline in my professional decisions.**				1	
9. **I would recommend this guideline for use in practice.**					1

Summary of Written Comments

The targeted reviewer feedback was supportive, with no suggestions for changing the guideline other than to note that the full publication of the Programme Etude Rein Cytokines (PERCY) Quattro trial was available (10). This evidence was available only in abstract form when the original literature search was done and the full report was published in December 2007, thus falling outside of the literature search dates of 1966 to November 2006. The search was updated to identify relevant literature up to May 2009. No relevant studies other than the PERCY Quattro trial (10) were found. Incorporation of the full report of the PERCY Quattro trial did not affect the results. Median survival data did not differ from those available from the abstract. Progression-free survival between the interferon and medroxyprogesterone acetate groups was 3.4 (range 3.0 to 5.6) versus 3.0 (range 2.9 to 3.6) months. The updated HR for overall survival for IFN-treated patients versus non-IFN-treated patients was 1.00 (95% CI 0.81 to 1.24).

Professional Consultation: One response was received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to three items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1		
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				1	
3. I would recommend this guideline for use in practice.				1	

Summary of Written Comments

The reviewer did not agree with the second recommendation, feeling too much weight was placed on older trials that were less well performed, and the doses used showed severe toxicity.

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