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Evidence-based Series 8-5 Version 2- EDUCATION AND INFORMATION 2013

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

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma

Members of the Melanoma Disease Site Group

An assessment conducted in November 2013 put Evidence-based Series (EBS) 8-5 Version 2 in the Education and Information. This means that the recommendations will no longer be maintained by 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) 8-5 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 Melanoma DSG page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/melanoma-ebs/

Release Date: September 15, 2011

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- Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev. 2007 Aug;33(5):484-496. Epub 2007 Jun 11. doi:10.1016/j.ctrv.2007.04.003.

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Evidence-based Series 8-5 Version 2

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version March 2006	1985 to 2006	Full Report	Peer review publication[1,2] Web publication	Not Applicable
Version 2 Sep 2011	2006 to 2010	New data found in Document Assessment & Review Tool	Updated Web publication	Guideline recommendations ENDORSED

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[1] Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a clinical practice guideline. Curr Oncol. 2007;14(1):21-6.
[2] Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev. 2007 Aug;33(5):484-496.

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Evidence-based Series 8-5 Version 2

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma

Guideline Review Summary

Review Date: August 4, 2010

The 2006 guideline recommendations are

ENDORSED

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

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OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2006. In June 2010, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Practice Guideline and the Systematic Review in this version are the same as in the March 2006 version.

Update Strategy

Using the Document Assessment & Review Tool, 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

Questions Considered

1. What is the role of single-agent interleukin-2 (IL-2) in the treatment of adults with metastatic melanoma? Primary outcomes of interest include objective response rates, complete response rates, duration of response, toxicity, and quality of life. Secondary outcomes of interest include progression-free survival and overall survival.
2. If there is a role for single-agent IL-2, what is the appropriate patient population to be considered for treatment?
3. If there is a role for single-agent IL-2, what is the appropriate dose and schedule?

4. What are the toxicities associated with IL-2?

Literature Search and New Evidence

The new search (March 2006 to June 2010) yielded eight relevant new publications (six abstracts and two full text publications) of eight studies, including one RCT. Results of these publications are shown in the Document Assessment & Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations for EBS 8-5; therefore, the Melanoma DSG **ENDORSED** the 2006 recommendations on single-agent interleukin-2 in the treatment of metastatic melanoma.

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Evidence-based Series #8-5: Section 1

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma: A Clinical Practice Guideline

T. Petrella, I. Quirt, S. Verma, A. Haynes, M. Charette, K. Bak, and members of the Melanoma Disease Site Group

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

Report Date: March 20, 2006

Please see the EBS 8-5 Version 2 Guideline Review Summary and the Document Assessment & Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: March 20, 2006

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Questions

1. What is the role of single-agent interleukin-2 (IL-2) in the treatment of adults with metastatic melanoma? Primary outcomes of interest include objective response rates, complete response rates, duration of response, toxicity, and quality of life. Secondary outcomes of interest include progression-free survival and overall survival.
2. If there is a role for single-agent IL-2, what is the appropriate patient population to be considered for treatment?
3. If there is a role for single-agent IL-2, what is the appropriate dose and schedule?
4. What are the toxicities associated with IL-2?

Recommendations

There are no studies that compare IL-2 to the current standard of care, dacarbazine (DTIC), or to placebo in the treatment of metastatic melanoma.

- After weighing and reviewing the evidence that does exist, the opinion of the Melanoma Disease Site Group is that high-dose IL-2 is a reasonable treatment option for a select group of patients with metastatic melanoma:
  - Patients should have a good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1), and a normal lactate dehydrogenase (LDH) level.

  - Patients should have less than three organs involved or have cutaneous and/or subcutaneous metastases only and no evidence of central nervous system metastases.

  In this select group of patients IL-2 treatment can produce durable complete remissions.
- The recommended dose and schedule of high-dose IL-2 is 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, for a maximum of 14 doses.
- If high-dose IL-2 is delivered, the recommendation is that it be done in a tertiary care facility with staff trained in the provision of this treatment with appropriate monitoring.
- To facilitate patient treatment and develop expertise in this therapeutic modality, the recommendation is that high-dose IL-2 programs be established in one or two centres in Ontario.

Qualifying Statements
- High dose IL-2 has similar response rates to our standard chemotherapy; however the low but durable complete response seen with IL-2 is very rare with chemotherapy and may lead to years of benefit for patients.
- Based on the available data assessing prognostic factors and patient selection, patients with non-visceral metastases and fewer metastatic sites have a much higher response rate. In these select patients, high dose Interleukin-2 may be considered first line therapy.
- Recommendations for this guideline are based largely on phase II data and very little phase III data due to the lack of availability of large randomized trials comparing IL-2 to DTIC or other chemotherapy. Further randomized data will not be available as there are currently no ongoing or planned randomized trials. IL-2 is currently widely used in the United States and is an approved therapy in both Canada and the United States.

Key Evidence
- There are no randomized controlled trials that compare high-dose IL-2 to the current standard of care, DTIC.
  - The only randomized controlled trials conducted to date have compared high-dose single-agent IL-2 to high-dose IL-2 in combination with either interferon or lymphokine-activated killer cells.
- Data from three randomized controlled trials has demonstrated that single-agent IL-2, when given in high doses, can elicit an objective response rate of 5% to 27% with complete responses in 0% to 4% of patients.
  - Similarly several noncomparative phase II trials of high-dose single-agent IL-2 have consistently reported objective response rates of 10% to 33% with complete responses ranging from 0% to 15%.
- High-dose IL-2, as a single agent or in combination with lymphokine-activated killer (LAK) calls, can elicit long-term responses in select patients.
  - The three randomized trials demonstrate that in the 0% to 11% of patients, who are complete responders, there have been consistent observations of long-term responses that range from 6 to 66+ months (median 27 months).
  - Complete responders in phase II trials have also demonstrated impressive long-term responses that range from 1.5 to 148 months (median 70 months).
  - No other therapy for metastatic melanoma offers the possibility for a durable complete remission.
- Several trials have investigated factors associated with response to IL-2. Those data show that carefully selected patients have the highest chance of response. Patients with a good performance status (ECOG 0-1) and a normal LDH level, as well as with less than three organs involved or cutaneous and/or subcutaneous metastases only have the highest

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probability of responding and achieving a durable complete response. That carefully selected group of patients should be considered for treatment with high-dose IL-2.

- The recommended dose and schedule of high-dose IL-2 is supported by the majority of trials as well as the National Cancer Institute.
  - The majority of trials of high-dose single-agent IL-2 used a dose and schedule of 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, for a maximum of 14 doses. The National Cancer Institute published guidelines for the safe administration of high-dose IL-2 in 2001 and recommended the above dose and schedule. In addition, the United States Food and Drug Administration approved the use of IL-2 for the treatment of patients with metastatic melanoma at that same dose and schedule.
- High-dose IL-2 should be delivered in a tertiary care facility with staff trained in the provision of this treatment with appropriate monitoring.
  - High-dose IL-2 therapy has considerable grade 3/4 toxicity. Three randomized controlled trials of high-dose IL-2 and eight noncomparative phase II trials of single-agent high-dose IL-2 have reported the following types of grade 3/4 adverse effects: gastrointestinal (range 0-76%), cardiovascular (range 0-74%), renal (range 0-87%), neurologic (range 0-29%), hematologic (range 0-71%), febrile neutropenia (range 4-88%), sepsis (range 0-63%) and hepatic (0-90%). Those toxicities are manageable with the use of available guidelines and trained staff.

Related Guidelines

The Program in Evidence-based Care's:

- Evidence-based Series Report #8-3: *Biochemotherapy for the Treatment of Metastatic Malignant Melanoma.* Please note that this guideline is currently under development and is not yet available on the Web site.
- Evidence-based Series Report #8-4: *Single-agent Temozolomide for the Treatment of Metastatic Melanoma.* Please note that this guideline is currently under development and is not yet available on the Web site.

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Evidence-based Series #8-5: Section 2

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma: A Systematic Review

T. Petrella, I. Quirt, S. Verma, A. Haynes, M. Charette, K. Bak, and members of the Melanoma Disease Site Group

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

Please see the EBS 8-5 Version 2 Guideline Review Summary and the Document Assessment & Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: March 20, 2006

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QUESTIONS

1. What is the role of single-agent interleukin-2 (IL-2) in the treatment of adults with metastatic melanoma? Primary outcomes of interest include objective response rates, complete response rates, duration of response, toxicity, and quality of life (QOL). Secondary outcomes of interest include progression-free survival and overall survival.
2. If there is a role for single-agent IL-2, what is the appropriate patient population to be considered for treatment?
3. If there is a role for single-agent IL-2, what is the appropriate dose and schedule?
4. What are the toxicities associated with IL-2?

INTRODUCTION

Melanoma incidence has been steadily increasing. In 2004, there were approximately 4200 cases of melanoma in Canada, and the estimated lifetime risk is approximately 1 in 80 for men and 1 in 94 for women (1). Though early detection, appropriate surgery, and adjuvant therapy have improved outcomes, at least one third of patients with early-stage disease will develop metastases. Patients with metastatic melanoma have a median survival of six to eight months, with only 5% surviving more than five years. Many agents have been investigated for antitumour activity in melanoma, although few have shown a response in more than 10% of patients. Dacarbazine (DTIC) has been compared to temozolomide, the

Dartmouth regimen (DTIC, cisplatin, carmustine, and tamoxifen) and to DTIC plus antisense therapy in three large randomized trials (2-4). To date, DTIC has not been compared to best supportive care. When compared to the Dartmouth regimen, DTIC had an overall response rate of 10.2% compared to 18.5% with the Dartmouth regimen (2). However, that result was not statistically significant (p=0.09), and there were no complete responders. Overall survival and median survival did not differ in the two arms (2). DTIC has also been compared to temozolomide (3), with a response rate of 12.1% versus 13.5% with temozolomide, a 3% complete response rate in both arms, a similar duration of response, and no difference in survival. A recently published abstract (4), that was the largest randomized study with DTIC published to date, with 771 patients, compared DTIC to DTIC with BCL-2 antisense. The overall response rate for single-agent DTIC was only 6.8% compared to 11.7% for DTIC plus BCL-2 antisense, however no real difference in survival was reported. The data from those three trials have made DTIC the accepted standard; however, response rates are low, durable responses are rare, and an impact on survival has never been shown. There is universal agreement that further research is critically needed.

Systemic approaches that have been systematically evaluated to date for metastatic disease include cytotoxic chemotherapy (single-agent and multi-drug combinations), vaccines, biochemotherapy, and cytokines such as interferon and IL-2. The latter, single-agent IL-2, has attracted much attention over the past several years. A number of randomized trials and many phase II trials have been completed and their results reported. Those results have generated much interest, particularly the durability of response in complete responders. Given the dismal survival of patients with metastatic melanoma and the limited availability of effective treatments, that durability of response with IL-2 treatment warranted closer examination of this approach by the Melanoma Disease Site Group (DSG).

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by two members of the PEBC Melanoma DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on IL-2 in metastatic melanoma. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of the clinical practice guideline (Section 1) developed by the Melanoma DSG. The 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

Searches were performed in the following databases: MEDLINE (1985 through March week 5, 2006), EMBASE (1985 through 2006 week 14), and the Cochrane Library (2006, Issue 1). "Melanoma" (Medical Subject Heading (MeSH) and text word) was combined with "interleukin-2" (MeSH and text word) or "IL-2" (text word). Those terms were then combined with search terms to locate practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and phase II trials.

In addition, the proceedings of the annual meeting of the American Society of Clinical Oncology (1997-2005) were searched for reports of newly completed or ongoing trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

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Inclusion Criteria

The following types of articles were selected for inclusion in this systematic review of the evidence:

1. Full reports or abstracts of randomized controlled trials or randomized phase II trials in which one trial arm involved single-agent IL-2 for patients with metastatic melanoma.
2. Full reports or abstracts of single-arm phase II trials of single-agent IL-2 for patients with metastatic melanoma, which were included because insufficient evidence was available from randomized controlled trials.
3. Meta-analyses of randomized controlled trials, systematic reviews and evidence-based practice guidelines.

Exclusion Criteria

1. Papers published in a language other than English were not considered due to limited resources for translation.
2. Phase I studies were not considered.
3. Reports that provided data for a sample of less than 10 patients with metastatic melanoma were excluded.

Synthesizing the Evidence

None of the randomized controlled trials compared single-agent IL-2 to standard therapy or to placebo. In addition, the randomized controlled trials included different regimens and doses of IL-2 as well as combining IL-2 with different agents (lymphokine-activated killer cells, interferon, and histamine dihydrochloride). Due to the heterogeneity between the randomized controlled trials, the Melanoma DSG decided against conducting a meta-analysis of the results.

RESULTS

Literature Search Results

One systematic review (5), five randomized trials comparing single-agent IL-2 versus IL-2 combination therapy (6-10) and 12 single arm phase II trials (11-23) were eligible for inclusion in this systematic review of the evidence. In addition, one QOL report for patients included in one of the randomized trials was identified (24).

Systematic Review

One systematic review with meta-analysis reported by Allen et al (5) was identified that evaluated the efficacy and safety of IL-2, chemotherapy, IL-2 + chemotherapy, IL-2 + interferon, and IL-2 + chemotherapy + interferon (biochemotherapy) for patients with metastatic melanoma.

Medline, Cancerlit and Current Contents® databases were searched and 154 fully published papers or published abstracts were located and analyzed for response, duration of response, and median survival. Comparative arms were included in eleven studies however not all were randomized. Data extracted from the treatment arms of multiple studies was pooled in a meta-analysis using both fixed and random effects models. Begg's hierarchical Bayes model was used to estimate the proportions of patients with CR or PR. The rate difference (RD) in response between treatment arms was calculated for nonrandomized, controlled studies with a comparator treatment arm. For uncontrolled studies the rate difference was estimated using Begg's Bayesian meta-analysis techniques. Sensitivity analyses were carried out using a logistic regression model to examine the influence of study level covariates on efficacy. The pooled results were weighted by treatment arm size and the efficacy outcomes of interest were calculated on an intent-to-treat basis.

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A total of 3,285 eligible patients were enrolled in 97 treatment arms of IL-2 as either a single agent, or in combination with chemotherapy, interferon, or biochemotherapy. The pooled objective response rate (complete response + partial response), in this patient population, was 24.6%, with a median duration of response of 8.2 months and a median overall survival of 9.6 months. The review authors also reported data on only 710 patients (23 treatment arms) who received single-agent IL-2. The pooled objective response rate was 14.3%, with a median duration of response of 8.0 months and median survival of 8.1 months. The authors concluded that objective response was significantly improved for IL-2 + chemotherapy or biochemotherapy compared to chemotherapy alone, single-agent IL-2, or IL-2 + interferon (Risk Difference, 16.7% ± 0.012, $p<0.001$). For the IL-2 + biochemotherapy regimen, high-dose IL-2 significantly improved objective response compared to low-dose IL-2 (45% versus 37%, respectively, $p=0.010$).

The systematic review reported by Allen et al (5) was complete, however, only up to September 1996. Additional trials of IL-2 including one randomized trial of low-dose IL-2 and several single-arm phase II trials of single-agent IL-2 have been published since the publication of that systematic review. Those new trials contain additional evidence that has not yet been analyzed together with the previously available evidence.

Randomized Trials

Trial Characteristics

No randomized trials of IL-2 alone compared to placebo or standard treatment were identified. Five randomized controlled trials of IL-2 alone, compared to IL-2 combination therapy were eligible for inclusion in this systematic review. Three randomized trials examined high-dose IL-2 (6-8), with doses of IL-2 ranging from 100,000 IU/kg to 6 MIU/m^2 given intravenously over 15 minutes every 8 hours. One randomized trial examined low-dose IL-2 (9), administered subcutaneously at 2 and 9 MIU/m^2. The final randomized trial examined IL-2 at a dose of 3 MIU/m^2 administered as a continuous intravenous infusion (10). The specific regimens for each trial are shown in Table 1.

Table 1. Randomized trials of IL-2: regimens.

First author, year (ref)	# patients (enrolled / evaluable)	IL-2 Regimen
Trials of High-dose IL-2		
Sparano, 1993 (6)	44/44	IL-2: 6 MIU/m^2 iv (15min) q8hr d1-5,15-19 (max. 28 doses)
	41/41	IL-2: 4.5 MIU/m^2 iv (15min) q8hr d1-5,15-19 IFN: 3 MIU/m^2 iv (15min) q8hr d1-5,15-19
Rosenberg, 1993 (7) NCI[a]	26/22	IL-2: 720,000 IU/kg iv q8hr d1-5,11-15
	28/27	IL-2: as above LAK: iv d11-15
McCabe, 1991 (8) [b] [abstract]	46/45	IL-2: 100,000 IU/kg iv q8hr d1-5,11-15
	52/49	IL-2: as above LAK: d11,12,14
Trials of Low-dose IL-2		
	153/153	IL-2: 9 MIU/m^2 sc bid d1,2 weeks 1,3; 2 MIU/m^2 sc bid d1-5 weeks 2,4

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First author, year (ref)	# patients (enrolled / evaluable)	IL-2 Regimen
Agarwala, 2001 (9)	152/152	IL-2: as above Histamine: 1 mg sc bid d1-5 weeks 1-4
Trials of IL-2 Administered by Continuous Intravenous Infusion		
Richards, 1990 (10) [abstract]	NR/33	IL-2: 3 MIU/m^2 civ d1-5,13-17,21-24,28-31
	NR/35	IL-2: as above LAK: d13-15

Note: bid = twice daily; d = day(s); hr = hour(s); IFN = interferon; IL-2 = interleukin-2; IU = International Units; iv = intravenous; civ = continuous intravenous infusion; LAK = lymphokine-activated killer cells; max. = maximum; min = minutes; MIU = Million International Units; NCI = National Cancer Institute; NR = not reported; q = every; ref = reference; sc = subcutaneously.
[a] Includes other cancer types; information in tables is for melanoma only.
[b] Reports on a subgroup of patients also included in the Atkins trial (13,14). Dose indicated in this trial differs from the dose indicated in the Atkins trial.

The characteristics of patients included in the randomized trials of IL-2 are shown in Table 2. Performance status was reported in all five randomized trials of IL-2 except for the trial reported by Richards et al (10). All three trials of high-dose IL-2 used the Eastern Cooperative Oncology Group (ECOG) performance status scale. Two trials included patients with ECOG PS 0-1 (6,8) and one trial included ECOG PS 0-2 (7). The randomized trial of low-dose IL-2 reported by Agarwala et al (9) used the World Health Organization (WHO) scale, with patients having PS 0-1.

Two trials reported on prior treatment for patients with melanoma (6,9). Prior chemotherapy was given to 22% to 26% of patients. Sparano et al (6) also reported that patients received prior immunotherapy and/or radiation therapy. Only two trials reported the sites of metastases (6,9). The most common sites were the lungs, liver, skin, soft tissue, and lymph nodes. Other sites of metastatic disease included bone, central nervous system, and abdomen. Lactate dehydrogenase was reported only in the low-dose IL-2 trial by Agarwala et al (9). All patients included in the trials of high-dose IL-2 were treated as in-patients (6-8). Conversely, patients included in the trial of low-dose IL-2 were treated as out-patients (9).

Table 2. Randomized trials of IL-2: Patient characteristics.

First author, year (ref)	Trt Arms (# eval pts)	Performance status (% of pts.)	Median Age (years)	Prior treatment specifics (% of pts)	Sites of metastases (% of pts)	LDH Level*	In/out-patient
Trials of High-dose IL-2							
Sparano, 1993 (6)	IL-2 (44)	ECOG 0, 66% ECOG 1, 34%	50	IMT, 5% CT, 23% RT, 18%	Skin, soft tissue, lymph nodes, 25%; lung, 23%; liver, 52%	NR	In-patient
	IL-2 + IFN (41)	ECOG 0, 61% ECOG 1, 39%	50	IMT, 7% CT, 22% RT, 24%	Skin, soft tissue, lymph nodes, 32%; lung, 29%; abdomen,14%; liver,25%		
Rosenberg, 1993 (7) NCI	IL-2 (22)	ECOG 0-2	NR	Melanoma pts NR	NR	NR	In-patient
	IL-2 + LAK (27)						

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First author, year (ref)	Trt Arms (# eval pts)	Performance status (% of pts.)	Median Age (years)	Prior treatment specifics (% of pts)	Sites of metastases (% of pts)	LDH Level*	In/out-patient
McCabe, 1991 (8) [abstract]	IL-2 (45)	ECOG 0,1	NR	NR	NR	NR	In-patient
	IL-2 + LAK (49)						
Trials of Low-dose IL-2							
Agarwala, 2002 (9)	IL-2 (153)	WHO 0, 68% WHO 1, 32%	56	CT, 26%	Soft tissue/lymph node, 15%; lung, 62%; liver, 42%; bone, 10%; CNS, 7%	<ULN 56% ≥ULN 37%	Out-patient
	IL-2 + HD (152)		53			<ULN 60% ≥ULN 34%	
Trials of IL-2 Administered as a Continuous Intravenous Infusion							
Richards, 1990 (10) [abstract]	IL-2 (33)	NR	NR	NR	NR	NR	NR
	IL-2 + LAK (35)						

Notes: CNS = central nervous system; CT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; eval = evaluable; HD = histamine dihydrochloride; IFN = interferon; IL-2 = interleukin-2; IMT = immunotherapy; LAK = lymphokine-activated killer cells; LDH = lactate dehydrogenase; NCI = National Cancer Institute; NR = not reported; pts = patients; ref = reference; RT = radiation therapy; Trt = treatment; ULN = upper limit of normal, where normal = 100-250 IU/L; WHO = World Health Organization.
* Lactate dehydrogenase was specifically assessed as this has been demonstrated to be an independent prognostic factor (26).

Outcome: response

Tumour response data as reported in the randomized trials of IL-2 can be found in Table 3. None of the randomized trials of IL-2 reported a significant difference in objective response rate between the treatment arms. The objective response rate for IL-2 alone ranged from 5%-27% in the trials of high-dose IL-2 (6-8). Low-dose IL-2 elicited an objective response rate of 2% in the trial reported by Agarwala et al (9), and IL-2 administered as a continuous intravenous infusion elicited an objective response rate of 9% (10). The objective response rate for IL-2 in combination with lymphokine-activated killer cells (LAK), interferon, or histamine dihydrochloride (HD) ranged from 5%-22%. The complete response rate for IL-2 alone or in combination ranged from 0-11%. None of the trials reported time to response data.

Sparano et al (6) reported median duration of response as 11.5 months (range, 2.0-15.7+ months). None of the other randomized trials reported data on duration of objective response. Rosenberg et al (7) reported that the patients in IL-2 alone arm had no complete responses while three patients who received IL-2 + LAK demonstrated complete responses with durations ranging from 52+ to 66+ months. McCabe et al (8) reported that two patients in the single agent IL-2 arm had complete responses with durations of six and 12 months. Three patients in the IL-2 + LAK arm also had complete responses with durations of 9, 24+ and 29+ months.

No trial reported data on median time to progression. However, Agarwala et al (9) reported that median time to progression was significantly longer for low-dose IL-2 + HD compared to low-dose IL-2 alone (p=0.038), although the actual median time to progression was not reported.

Outcome: overall survival

Survival data for patients in the randomized trials of IL-2 can be found in Table 3. Overall survival was reported in two of the high-dose IL-2 trials (6, 7) and in the low-dose IL-

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2 trial (9). None of the trials reported statistically significant differences in overall survival between the treatment arms.

In the Sparano et al (6) trial patients receiving single agent IL-2 demonstrated a median survival of 10.2 months while patients receiving the IL-2/IFN combination treatment showed a median survival of 9.7 months. Rosenberg et al (7) reported a trend towards improved survival for melanoma patients treated with IL-2 plus LAK cells compared to patients treated with single agent IL-2. The two year survival for patients treated with IL-2 plus LAK cells was 32% versus 15% for patients treated with single agent IL-2. Four year survival for this population was reported to be 18% and 4%, respectively. However, the validity of this trend needs to be tested with a larger patient population.

A survival trend was also noted in the low dose trial reported by Agarwala et al (9), however a statistically significant difference was not observed. Although a subgroup analysis of melanoma patients with liver involvement has demonstrated a statistically significant survival benefit for patients treated with IL-2 in combination with histamine (p = 0.008).

Table 3. Randomized trials of IL-2: tumour response and overall survival.

First author, year (ref)	Arms	# of eval pts	CR/PR (# of pts)	Objective response rate (CR +PR)	Median duration of response (CR + PR) (mos)	Duration of CR (mos)	Median survival (mos)	Median time to progression (mos)
Trials of High-dose IL-2								
Sparano, 1993 (6)	IL-2	44	0/2	5%	PRs: 11.5 (range 2.0 to 15.7+)	0	10.2	NR
	IL-2 + IFN	41	0/4	10% p=0.30			9.7 p=NS	
Rosenberg, 1993 (7) NCI	IL-2	22	0/6	27%	NR	0	2-yr: 15%	NR
	IL-2 + LAK	27	3/3	22%		66+, 66+, 52+	2-yr: 32% p=0.064	
McCabe, 1991 (8) [abstract]	IL-2	45	2/5	16%	NR	6,12	NR	NR
	IL-2 + LAK	49	3/3	12%		9, 24+,29+		
Trials of Low-dose IL-2								
Agarwala, 2002 (9)	IL-2	153	2/1	2%	NR	NR	8.2	p=0.038 (in favour of IL-2+HD, data NR)
	IL-2 + HD	152	3/4	5%			9.1 p=0.125	
Trials of IL-2 Administered as a Continuous Intravenous Infusion								
Richards, 1990 (10) [abstract]	IL-2	33	0/3	9%	NR	NA	NR	NR
	IL-2 + LAK	35	0/2	6%				

NOTES: CR = complete response; eval = evaluable; HD = histamine dihydrochloride; IFN = interferon; IL-2 = interleukin-2; LAK = lymphokine-activated killer cells; mos = months; NA = not applicable; NCI = National Cancer Institute; NR = not reported; NS = not significant; PR = partial response; pts = patients; ref = reference.

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Outcome: toxicity

Grade 3/4 toxicity data for patients in the randomized trials of IL-2 can be found in Table 4. Richards et al (10) did not report any data on adverse effects for patients that received IL-2 alone or in combination with LAK. McCabe et al (8) did not report data on adverse effects except on the total number of toxic deaths.

For the trials of high-dose IL-2, both Sparano et al (6) and Rosenberg et al (7) reported high rates of the following types of grade 3/4 adverse effects: gastrointestinal, cardiovascular (especially hypotension), renal, neurologic, hematologic, and febrile neutropenia and sepsis. However, as Rosenberg et al pointed out, the majority of the toxic effects disappeared shortly after the administration of IL-2 was discontinued (7). There were a total of 13 toxic deaths out of a total of 347 patients in the three trials of high-dose IL-2 that reported on that outcome (6-8).

The low-dose IL-2 trial (9) reported much lower rates of grade 3/4 toxicities than the trials of high-dose IL-2 and the treatment was administered on an outpatient basis. The most frequent grade 3/4 toxicity was nausea in the IL-2 alone arm (8% of 153 patients), and febrile neutropenia in the IL-2 + HD arm (8% of 152 patients). The trial authors did not report data on the number of toxic deaths.

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Table 4. Randomized trials of IL-2: grade 3 or 4 toxicity.

First author, year (Ref)	Arms	# of pts	GI		Cardiovascular			Renal - creatinine (%)	Hepatic		Neurologic		Hematologic			Febrile neut (%)	Sepsis (%)	Toxic deaths (# of pts)
			N/V (%)	Dr (%)	Hypo-tension (%)	Arr (%)	Isc / MI (%)		Alk Phos (%)	Bili (%)	Dis/ Som (%)	Coma (%)	Anemia with transfusion (%)	WBC (%)	Thromb (%)			
Trials of High-dose IL-2																		
Sparano, 1993 (6)	IL-2	44	16	25	49	NR	9	41	18	11	27	2	NR	30	16	48	2	2
	IL-2 + IFN	41	20	17	51	NR	0	39	29	0	29	0	NR	29 Neut	20	51	7	1
Rosenberg, 1993 (7)	IL-2	125[a]	76	66	61	7	1	80[b]	NR	88	26/13[c]	4	42	NR	50	NR	4	6
	IL-2 + LAK	137[a]	75	69	74	9	2	87[b]	NR	90	25/15[c]	4	71	NR	66	NR	7	
McCabe, 1991 (8)	IL-2	46	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4
	IL-2 + LAK	52																
Trials of Low-dose IL-2																		
Agarwala, 2002 (9)	IL-2	153	8/5	3	1	0[d]	0	0	1	2	3/3	4	4[e]	NR	1	7	0	NR
	IL-2 + HD	152	7/6	1	1	1[d]	<1	0	1	1	2/2	0	2[e]	NR	<1	8	<1	NR
Trials of IL-2 Administered as a Continuous Intravenous Infusion																		
Richards, 1990 (10) [abstract]	IL-2	33	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	IL-2 + LAK	35																

Notes: Alk Phos = alkaline phosphatase; Arr = arrhythmia; Bili = bilirubin; Dis = disorientation/confusion/dizziness; Dr = diarrhea; GI = gastrointestinal; HD = histamine dihydrochloride; IFN = interferon; IL-2 = interleukin-2; Isc = ischemia; LAK = lymphokine-activated killer cells; MI = myocardial infarction; N/V = nausea / vomiting; Neut = neutropenia; NR = not reported; pt(s) = patient(s); ref = reference; Som = somnolence; Thromb = thrombocytopenia; WBC = white blood cells.

[a] Number of cycles given to 85 and 79 patients in the IL-2 and IL-2 + LAK arms, respectively.

[b] Creatinine >2.1 mg/dL

[c] Authors did not report toxicity grade for disorientation or somnolence.

[d] Tachycardia.

[e] Grade 3 or 4 anemia reported; unknown whether patients had transfusions.

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Quality of life

Quality of life was examined only for patients in the randomized trial of low-dose IL-2 with or without HD reported by Agarwala et al (9). Data on QOL were collected and reported by Beusterien et al (24) in conjunction with that randomized trial. Quality of life data were collected prior to initiation of IL-2 therapy (baseline) and after every six-week cycle. The QOL survey included the Quality of Well Being-Self Administered (QWB-SA) questionnaire, an Overall State of Health item, and a General Health Perception item. The Overall State of Health item asked patients to rate their health over the preceding three day period on a scale from zero (least desirable state of health) to 100 (perfect health), and the General Health Perception item asked patients to rate their health on a scale from one (excellent) to five (poor). No significant differences were reported between the single-agent IL-2 arm and the combination treatment for the Overall State of Health or General Health Perception items.

The QWB-SA questionnaire included data for the following; symptom/complex, mobility, physical activity, and self-care – usual activity. Scores on the QWB-SA ranged from 0.0 (death) to 1.0 (optimum functioning without symptoms). Scores were calculated based on whether symptoms or problems were present one, two, and/or three days before filling out the questionnaire. Patients that died prior to completion of all cycles of therapy were assigned a QWB-SA score of 0.0 for all remaining treatment cycles. From a total of 305 randomized patients, 301 (98.7%) completed at least one QWB-SA questionnaire (IL-2 alone arm, 151 patients; IL-2 + HD, 150 patients). The IL-2 alone arm and the IL-2 + HD arm were similar in terms of missing data (34.9% and 33.4% missing questionnaires, respectively; p=0.419). The mean baseline QWB-SA score was 0.60 for both groups. The change in QWB-SA scores over time slightly favoured the IL-2 + HD group compared to the IL-2 alone group, however the difference was not statistically significant (p=0.511). Median quality-adjusted survival was longer in the IL-2 + HD arm compared to the IL-2 alone arm (105.6 days versus 74.3 days, respectively; p=0.007).

The QWB-SA data were also provided for a subgroup of patients that had liver metastases. Liver metastases were present prior to initiation of therapy in 73 of the 151 patients (48.3%) that completed at least one QWB-SA questionnaire in the IL-2 alone arm and in 53 of the 150 patients (35.3%) in the IL-2 + HD arm. The change in QWB-SA scores over time significantly favoured the IL-2 + HD arm compared to the IL-2 alone arm (p=0.018). Statistically significant differences in QWB-SA scores favouring the IL-2 + HD arm were present after cycle 2 (p=0.011), cycle 3 (p=0.002), cycle 4 (p=0.044), and cycle 5 (p=0.033), with differences in scores ranging from 0.11 to 0.16. Median quality-adjusted survival was longer in the IL-2 + HD arm compared to the IL-2 alone arm (113.0 days versus 62.8 days, respectively; p=0.011).

Phase II Trials

Overview

Twelve single-arm phase II trials were identified that examined the use of single-agent IL-2 and were included to obtain further evidence of objective tumour response, complete response, and durability of complete response as well as further information on toxicity and toxicity outcomes. Eight of those phase II trials administered high-dose IL-2 (11-19), and the remaining four trials administered IL-2 as a continuous intravenous infusion (20-23). The specific regimens for each trial are shown in Table 5.

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Table 5. Single-arm phase II trials of IL-2: regimens.

First author, year (ref)	# pts (enrolled / evaluable)	IL-2 Regimen
Trials of High-dose IL-2		
Agarwala, 2005 (11) [abstract]	26/26	600,000 IU/kg/dose (max 14 doses/cycle)
Pappo, 2001 (12)	21/21	720,000 IU/kg iv (15 min) q8hr for up to 5d (max 14 doses)
Atkins, 1999, 2000 (13,14)	270/270[a]	600,000 or 720,000 IU/kg iv (15 min) q8hr for up to 5d (max 14 doses)
Rosenberg, 1998 (15) [a]	182/182	720,000 IU/kg iv (15 min) q8hr for up to 5d (max15 doses)
Whitehead, 1991 (16)	46/42	60 MIU/m^2/d iv (15min) Mon, Wed, Fri[c]
Parkinson, 1990 (17) [b]	47/46	100,000 IU/kg/d iv (15min) q8hr d1-5[d]
Rosenberg, 1989 (18) [a]	60/42	100,000 IU/kg iv q8hr d1-5,14-18
Thatcher, 1989 (19)[e]	16/16	11 MIU/m^2/d is (1hr) d1, iv (1hr) d1 (4hr after is dose), d3,5,7
Trials of IL-2 Administered by Continuous Intravenous Infusion		
Legha, 1996 (20)	33/31	12 MIU/m^2 civ d1-4 (96 hrs) for 4 weeks
Vlasveld, 1994 (21)[b]	15/15	1.8 MIU/m^2 civ (24 hrs) for 3 weeks
Dorval, 1992 (22)	24/24	20 MIU/m^2 civ d1-5,15-18,29-31
Paciucci, 1992 (23)[b] Study 2	12/12	3.4 MIU/m^2 civ d1-6

Notes: # = number; civ = continuous intravenous infusion; d = day; hr = hour; IL-2 = interleukin-2; IU = International Units; iv = intravenous; is = intrasplenically; MIU = Million International Units; max = maximum; min = minutes; pts = patients; q = every; NCI = National Cancer Institute; ref = reference; SWOG = Southwest Oncology Group.

[a] Includes other cancer types; information in tables is for melanoma only.

[b] Reports on a subgroup of patients also included in the Atkins trial (13,14). Dose indicated in this trial differs from the dose indicated in the Atkins trial.

[c] The initial dose was decreased to 36 MIU/m^2/d after 16 patients were treated because of toxic effects.

[d] Nine patients treated at the University of Maryland Cancer Centre might have received 15 doses of IL-2 per course. For all other patients, the maximum was 14 doses.

[e] Only the results of the phase II study are presented.

The characteristics of patients included in the non-comparative phase II trials of single-agent IL-2 are shown in Table 6. All of those trials reported patient PS, except for the trial reported by Pappo et al (12). Six trials used the ECOG PS scale (13-15,17,18,20,22), one trial, each, used the Southwest Oncology Group (SWOG) scale (16), Karnofsky scale (19), or Cancer and Leukemia Group B (CALGB) scale (23), and two trials did not report the scale used (11,21). All patients were reported as PS 0-2 (scale: ECOG, SWOG, CALGB, or not reported), except for patients in the trials by Rosenberg et al (18) who were reported as ECOG PS 0-3 and in the trial by Thatcher et al (19) who were reported as Karnofsky PS ≥50. Nine trials reported on prior treatment (11-17,19-21). Only one of those trials excluded patients that had received prior treatment (16). The remaining eight trials reported that patients had received prior chemotherapy, hormonal therapy, immunotherapy, limb perfusion, radiation therapy, surgery, or various combinations of those modalities. The percentages of patients that received prior treatment ranged from 1% of 182 patients that received hormonal therapy (15) to 100% of 26 patients that received biochemotherapy (11).

Nine trials reported the sites of metastases in patients receiving single-agent IL-2 (12-16,19-23). Sites of metastatic disease included the lungs, peritoneum, liver, lymph nodes, soft tissue, adrenal gland, bone, breasts, or gastrointestinal tract. None of the trials reported on lactate dehydrogenase. Six trials of high-dose single-agent IL-2 reported that patients were treated in an in-patient setting (11,12,15-17,19). One of the trials that administered single-agent IL-2 as a continuous intravenous infusion treated patients on an in-patient basis

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(20), one trial treated patients on an out-patient basis (21), and the two remaining trials did not report on treatment setting (22,23).

Table 6. Single-arm phase II trials of IL-2: patient characteristics.

First author, year (ref)	# of eval pts	Performance Status (% of pts)	Median Age (yrs)	Prior treatment specifics (% of pts)	Sites of metastases (% of pts)	Inpatient / Outpatient
Trials of High-dose IL-2						
Agarwala, 2005 (11) [abstract]	26	0-1, 100%	44	bioCT, 100%	NR	Inpatient
Pappo, 2001 (12)	21	NR	46	CT, RT, or IMT, 91%	Dermal/sub-dermal, 52%; lung, 52%; peritoneal, 28%; liver, 19%	Inpatient
Atkins, 1999, 2000 (13,14)	270[a]	ECOG 0, 71% ECOG 1, 27% ECOG 2, 2%	42	CT, 14% IMT, 19% HT, 1% CM, 12%	Visceral, 69% Non-visceral, 31%	NR
Rosenberg, 1998 (15) NCI	182	ECOG 0, 81% ECOG 1, 16% ECOG 2, 3%	NR	Prior IL-2 therapy excluded. None, 1%; Sx, 97%; CT, 26%; RT, 16%; HT 1%; any 2 or more, 53%; any 3 or more, 20%	lung, lymph nodes, liver, intraperitoneal, (percentages not available)	Inpatient
Whitehead, 1991 (16) SWOG	42	SWOG 0, 60% SWOG 1, 40%	51	No prior treatment allowed	Non-visceral, 17% Visceral, 83%	Inpatient for first week of treatment
Parkinson, 1990 (17)	46	ECOG 0, 57% ECOG 1, 43%	Range 20-71	IMT, 17% CT, 17% RT, 13%	NR	Inpatient
Rosenberg, 1989 (18)	42	ECOG 0-3	NR	NR	NR	NR
Thatcher, 1989 (19)	16	Karnofsky score ≥50	Range 30-69	CT, RT (%NR)	Visceral, 88% Non-visceral, 12%	Inpatient
Trials of IL-2 Administered as a Continuous Intravenous Infusion						
Legha, 1996 (20)	31	ECOG 0, 70% ECOG 1, 30%	44	Prior IL-2 therapy excluded. None, 3% CT, 97% HT, 18% IMT, 50% RT, 21%	soft tissue only, 33% lung +/- soft tissue, 21% visceral, 46%	Inpatient
Vlasveld, 1994 (21)	15	0, 93% 1, 7%	51	Sx, 100% RT, 27% limb perfusion, 20%	skin, 73% lung, 20% liver, 13% lymph nodes, 7%	Outpatient
Dorval, 1992 (22)	24	ECOG 0, 71% ECOG 1, 29%	Range 19-62	NR	liver, 13%; adrenal gland, 8%; lymph nodes, 54%; cutaneous, 67%; subcutaneous, 8%; bone, 4%; lung, 17%; peritoneal carcinomatosis, 4%; breast, 4%, not specified, 4%	NR
Paciucci, 1992 (23) Study 2	12	CALGB 0-2	50	NR	lymph nodes, lung, liver, subcutaneous, skin, bone, gastrointestinal (% NR)	NR

Notes: bioCT = biochemotherapy; CALGB = Cancer and Leukemia Group B; CM = combination therapy; CT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; HT = hormonal therapy; IL-2 = interleukin-2; IMT = immunotherapy; NCI = National Cancer Institute; NR = not reported; pts = patients; ref = reference; RT = radiation therapy; SWOG = Southwest Oncology Group; Sx = surgery.

[a] Includes 270 patients treated on eight phase II trials, including Parkinson (17) and McCabe (8).

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Outcome: response

Tumour response data that was reported for patients in the non-comparative phase II trials of single-agent IL-2 can be found in Table 7. Atkins et al (13,14) combined and re-analyzed the results of eight separate clinical trials conducted between 1985 and 1993 that included 270 assessable patients. The objective response rate was 16% with a median time-to-progression of 13.1 months. Partial responses were observed on 10% of patients and complete responses were evident in 6%. Updated results published by Atkins et al in 2000 (14), reported a long-term duration of complete response of 59 months however, the median duration of complete responses had not yet been reached in this patient population. Similarly, Rosenberg et al (15) reported a trial on 182 patients, who demonstrated an objective response rate of 15% and a median duration of objective response of 16 months. The complete response rate was 7% with a median duration of complete response that had not yet been reached at a minimum follow-up of 70 months.

Objective response rates for the other six trials of high-dose single-agent IL-2 ranged from 10%-33% (11,12,16-19). Median duration of objective response was reported only by Parkinson et al (17) and Thatcher et al (19) as 8 months and 3.5 months, respectively. The complete response rate for the other six trials of high-dose single-agent IL-2 ranged from 0-15% (11,12,16-19). Duration of complete response was reported as ranging from four months to 148+ months in those trials.

All four complete responders reported by Agarwala et al had metastases to skin, subcutaneous tissue, and/or to distant lymph nodes (11). The single complete responder reported by Pappo et al had subcutaneous and lymphatic tissue metastases (12). Thirteen of 17 complete responders reported by Atkins et al had metastases involving the skin, lymph nodes, and/or the lungs (13,14). Eight of 12 complete responders reported by Rosenberg et al had lymphatic, lung, cutaneous and/or subcutaneous tissue metastases (15). Time to response was reported in only two trials, with Whitehead et al (16) reporting that four partial responses occurred between days 17 and 75, and Parkinson et al (17) reporting that all 10 objective responses occurred within 12 weeks of the first treatment. Median time to progression was 13.1 months in the trial reported by Atkins et al (13,14). None of the other trials of high-dose single-agent IL-2 reported on time to progression.

Objective response rates ranged from 0-58% in the four trials of IL-2 administered as a continuous infusion (20-23). The median duration of objective response was reported in two trials as 1.7 months and six months (20,22). The complete response rate ranged from 0-17% in all four trials. Duration of complete response was 18 months for the one patient with a complete response in the trial reported by Legha et al (20). Median time to progression was not reported in any of the three trials that reported patients that had an objective response.

Outcome: overall survival

Survival data for patients in the phase II trials of single-agent IL-2 can be found in Table 7. Median overall survival ranged from 9.8 months to 12.0 months in the three trials of high-dose IL-2 that reported on that outcome (11,13,14,16). Legha et al (20) reported a median overall survival of 9.7 months for 31 patients that received IL-2 administered as a continuous infusion. None of the other trials reported on overall survival.

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Table 7. Single-arm phase II trials of IL-2: tumour response and overall survival.

First author, year (ref)	# of eval pts	CR/PR (# of pts)	Objective response rate (CR + PR)	Time to response	Median duration of response (CR + PR) (months)	Duration of CR (months)	Median survival (months)	Median time to progression (months)
Trials of High-dose IL-2								
Agarwala, 2005 (11) [abstract]	26	4/1	19%	NR	NR	4,4,5,12+	9.8	NR
Pappo, 2001 (12)	21	1/6	33%	NR	NR	17	NR	NR
Atkins, 1999, 2000 (13,14)	270[a]	17/26	16%	NR	8.9 PR: 5.9	Median: not reached (range 1.5->122)	12.0	13.1
Rosenberg, 1998 (15) NCI[b]	182	12/15	15%	NR	16 PR: 7	12, 16, 70+, 71+, 71+, 80+, 84+, 91+, 93+, 95+, 96+, 148+ (at median follow-up of 85.2 months)	NR	NR
Whitehead, 1991 (16) SWOG	42	0/4	10% (95% CI, 3-23%)	Responses occurred on d17, 25, 49, 75	NR	NA	9.9	NR
Parkinson, 1990 (17)	46	2/8	22%	within 12w	9	14,20+	NR	NR
Rosenberg, 1989 (18)	42	0/10	24%	NR	NR (range 2-41+)	NA	NR	NR
Thatcher, 1989 (19)	16	0/2	13%	NR	3.5 (range 3-4)	NA	NR	NR
Trials of IL-2 Administered as a Continuous Intravenous Infusion								
Legha, 1996 (20)	31	1/6	22% (95% CI, 10% to 41%)	NR	6 (range 4-18)	18	9.7 (range 1-56+)	NR
Vlasveld, 1994 (21)	15	0/0	0%	NA	NA	NA	NR	NA
Dorval, 1992 (22)	24	0/8	33%	NR	1.7 (range 6w to 5 months)	NA	NR	NR
Paciucci, 1992 (23) Study 2	12	2/5	58%	NR	4 months across all 3 studies	NR	NR	NR

Notes: # = number; CI = confidence interval; CR = complete response; d = day; Eval = evaluable; IL-2 = interleukin-2; NA = not applicable; NCI = National Cancer Institute; NR = not reported; PR = partial response; pt(s) = patient(s); ref = reference; SWOG = Southwest Oncology Group; w = weeks.

[a] Includes 270 patients treated on eight phase II trials, including Parkinson (17) and McCabe (8).

[b] The following parameters were identified as significantly associated with complete response to treatment with IL-2 (numbers include 182 patients with metastatic melanoma and 227 patients with metastatic renal cancer): prior immunotherapy – 31/33 complete responders had no prior immunotherapy vs. 2/33 complete responders who did have prior immunotherapy (p=0.009); total IL-2 in first course: mean 11,171 IU/kg +/- 624 for complete responders vs. 9710 IU/kg +/- 183 for noncomplete responders (p=0.024); maximum lymphocytes (per mm^3): 8048 +/- 900 for complete responders vs. 6514 +/- 668 for noncomplete responders (p=0.017).

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Outcome: toxicity

Grade 3/4 toxicities for patients included in the single-arm phase II trials of single-agent IL-2 can be found in Table 8. The trials of high-dose IL-2 reported similar grade 3/4 toxicities to those reported in the randomized trials of high-dose IL-2. Both Pappo et al (12) and Rosenberg et al (15) reported that the toxic effects of treatment were similar to those reported in the past, and in the trials of high-dose IL-2 identified in this report. A number of studies has pointed out that adverse events resulting form IL-2 treatment are quite transient and tend to ceased once the treatment is discontinued (12, 15,16,18,19). Rosenberg el al concluded that over the years the safety of IL-2 administration has increased significantly. There were 16 toxic deaths among 948 patients in six phase II trials of high-dose IL-2 that reported on that outcome (12-18).

The single-arm phase II trials of IL-2 administered as a continuous infusion also reported similar rates of grade 3/4 toxicities as those reported in the high-dose IL-2 trials. Vlasveld et al (21) was the only identified trial that reported that no patients experienced grade 3/4 hypotension. However, the trial authors reported that 87% of patients experienced fatigue; data for other toxicities were not reported. Paciucci et al (23) reported that toxicities were substantial however the authors did not provide further details. Legha et al (20) reported only one toxic death among 33 patients. None of the other phase II continuous infusion IL-2 trials reported on the number of toxic deaths.

Quality of life

None of the identified non-comparative phase II trials of single-agent IL-2 included measures of QOL.

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Table 8. Single-arm phase II trials of IL-2: grade 3 or 4 toxicity.

First author, year (Ref)	# of pts	GI		Cardiovascular			Renal - creatinine (%)	Hepatic		Neurologic		Hematologic			Febrile neut (%)	Sepsis (%)	Toxic deaths (# of pts)
		N/V (%)	Dr (%)	Hypo-tension (%)	Arr (%)	Isc / MI (%)		Alk Phos (%)	Bili (%)	Dis/ Som (%)	Coma (%)	Anemia with transfusion (%)	WBC (%)	Thromb (%)			
Trials of High-dose IL-2																	
Agarwala, 2005 (11) [abstract]	26	NR	4	15	19[a]	NR	NR	NR	42	NR	NR[b]	NR	NR	27	NR	NR	NR
Pappo, 2001 (12)	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1
Atkins, 1999 & 2000 (13,14)	270	6/37	32	45	3[a]	3/1	1	2	9	13/3	1	2[c]	2 Leuk	17	19	2	6
Rosenberg, 1998 (15) NCI	409[d]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4
Whitehead, 1991 (16) SWOG	46	11	4	26	2	NR	7[e]	11[f]	2	2	NR[g]	NR	NR	2	4	NR	0
Parkinson, 1990 (17)	47	28	23	72	4	8	32[h]	17	17	21/13	2	NR	13 Neut	28	13	7	1
Rosenberg, 1989 (18)	236[i]	69	61	50	6	4	74	NR	85	22/12	4	44	NR	47	NR	6	4
Thatcher, 1989 (19)	36[k]	6	0	17	NR	NR	0	NR	0	0	0	1	0	0	50	NR	NR
Trials of IL-2 Administered as a Continuous Intravenous Infusion																	
Legha, 1996 (20)	33	31	28	18	12	NR	12	NR	33	0	NR	34[c]	60 Neut	25	31	NR	1
Vlasveld, 1994 (21)	23[d]	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dorval, 1992 (22)	24	NR	NR	54	NR	4	13	NR	13	NR	NR	38[c]	0	13	88	63	NR
Paciucci, 1992 (23) Study 2	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Notes: # = number; Alk Phos = alkaline phosphatase; Arr = arrhythmia; Bili = bilirubin; CNS = central nervous system; Dis = disorientation/confusion/dizziness; Dr = diarrhea; GI = gastrointestinal; IL-2 = interleukin-2; Isc = ischemia; Leuk = leukopenia; MI = myocardial infarction; NCI = National Cancer Institute; N/V = nausea / vomiting; Neut = neutropenia; NR = not reported; pts = patients; ref = reference; Som = somnolence; SWOG = Southwest Oncology Group; Thromb = thrombocytopenia; WBC = white blood cells.

[a] Tachycardia.

[b] 2 of 26 patients with grade 3 neurological toxicity

[c] Unknown whether patients had transfusion.

[d] Not all patients had melanoma - adverse effects reported as a percentage of total patients in the study.

[e] "Renal – other" adverse effects.

[f] "Hepatic – enzyme" adverse effects.

[g] 2 of 46 patients (4%) with grade 3/4 general neurologic toxicity.

[h] Creatinine > 5.1x normal.

[i] Number of courses given to 155 patients total (60 melanoma patients – toxicity data not reported separately from other patients).

[j] Creatinine > 2.1

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DISCUSSION

Metastatic melanoma is known to be one of the most resistant forms of cancer and as a result is a devastating illness lacking effective therapies. Currently DTIC and IL-2 are the only two agents approved in the United States as first-line therapy for stage IV melanoma. Both regimens have demonstrated an objective response rate well below 20%. DTIC, along with other conventional chemotherapy regimens, such as temozolomide or the Dartmouth regimen, demonstrate results similar to IL-2, producing infrequent complete responses and objective responses ranging from 6.8 to 18.5%. To date, no single drug, combination chemotherapy or biotherapy compound, has demonstrated an overall survival benefit in a randomized clinical trial. Given the limited effective treatments available, along with the dismal survival of patients with metastatic melanoma, treatment with IL-2 warrants a closer evaluation.

Our analysis of the available literature identified a systematic review and meta-analysis of high-dose IL-2 (5) which presented data comparable to the case record-based review published by Keilholz et al (25). Both of those reviews reported similar response rates; 14.3% and 14.9%, respectively when IL-2 was used as a single agent. The response rate in both reviews was defined as complete responses plus partial responses, where the complete responders were not separated out. This response rate is similar to what is seen with single agent chemotherapy. The median survival was 8.1 months and 7.5 months, respectively, which is consistent with the median survival for metastatic melanoma with best supportive care.

None of the identified studies assessed IL-2 versus DTIC or any other single agent chemotherapy. Interleukin-2 can be administered using several dosing regimens however; none of the studies directly compared the different dosing schedules. The authors of this report divided the trials according to dose: high dose IL-2 (100,000 to 720,000IU/kg intravenously over 15 minutes every 8 hours for a maximum of 14 doses), low-dose IL-2 (2 to 9MIU/m^2 subcutaneously) and IL-2 administered as a continuous infusion (1.8MIU/m^2/d to 20MIU/m^2/d continuous intravenous infusion).

The three randomized trials (6-8) of high-dose IL-2 reported varying objective response rates from 5% to 27% with complete response rates for IL-2 alone or in combination ranging from 0-11%. Although only the trial reported by McCabe et al (8) had two complete responses in patients receiving IL-2 alone and both responses were of short duration (6 and 12 months). None of these trials showed a statistically significant improvement in overall survival or progression free survival.

There were eight phase II trials assessing high dose IL-2. The results of eight separate clinical trials of 270 assessable patients, conducted between 1985 and 1993, were combined and re-analyzed by Atkins et al (13,14). The authors reported an objective response rate of 16% with a median duration of response of 8.9 months. The complete response rate was 6%, with the median duration of complete response not yet reached, and with a minimum follow-up of 59 months. The trial reported by Rosenberg et al (15) included 182 assessable patients and supported the findings by Atkins et al (13,14). The Rosenberg trial (15) reported a complete response rate of 7% with a median duration of complete response that had not been reached at a minimum follow-up of 70 months. The other six trials involved smaller numbers of patients with three of those trials having reported seven patients with complete responses, with durations ranging from 4 to more than 20 months (11,12,17). The majority of complete responses in those trials were seen in patients with skin, lymph node, or lung involvement.

A randomized trial reported by Agarwala et al (9) assessed the benefit of low dose IL-2 with and without histamine. The authors reported an improvement in survival for patients with liver metastases with the combination of IL-2 and histamine compared to IL-2 alone. Further trials to confirm these results are underway. This systematic review also located four

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single-arm trials of continuous infusion IL-2 which reported objective response rates varying from 0% to 58% (20-23). Complete responses were reported in two trials with rates of 3.2% (20) and 16.7% (23). These inconsistent results may be partly explained by the small sample sizes and patient selection differences.

Based on the identified evidence, high dose IL-2 as a single-agent or in combination with other agents provides little benefit with no improvement in survival. However, this trend is similar to numerous chemotherapeutic and immunological drug combinations that have failed to demonstrate a significant benefit in overall survival. The objective response rate seen with high-dose IL-2 treatment is similar to that seen with conventional chemotherapy and interferon in metastatic melanoma. However, the duration of complete response seen in phase II trials is impressive. An update of 270 patients with 43 responders by Atkins et al (14) reported a median duration of complete response of more than 59 months. This suggests a trend towards observed heightened survival in those who respond.

The identified trials included a heterogeneous population of patients with regard to disease sites, bulk of disease, performance status and prior treatments. Several studies have investigated factors associated with response to high dose IL-2 (27,28). In a retrospective review of 374 patients by Phan et al (27) patients with only subcutaneous and/or cutaneous metastases had a significantly higher response rate than patients with other sites of metastases (53.6% versus 12.4%, p=0.000001). Other factors such as high lymphocyte count post therapy, and development of vitiligo were associated with antitumour response to IL-2 therapy (27). Keilholz et al (25) performed a univariate analysis of pre-treatment factors and reported that ECOG performance status, number of involved organs, site of metastases and serum LDH all predicted for survival (p=0.0001). Therefore, patients with a good performance status (ECOG 0 or 1), less than 3 organs involved, cutaneous, and/or subcutaneous metastases only, and a normal LDH would have the highest probability of responding and should be considered for IL-2 therapy. Prior exposure to Interferon therapy also lowered the response rate when compared to interferon naïve patients, 21% versus 13% respectively, but this was not statistically significant (28). None of the identified trials were sufficiently powered to examine specific subsets of patients; however, when looking at the characteristics of the complete responders, all but 4 patients in the trials had skin, lymphatic, or lung metastases.

The objective response rate or complete response rate data from the trials of continuous infusion IL-2 were not consistent with the rates reported in the trials of high dose IL-2. High-dose IL-2 shows impressive durable complete responses that are consistent across studies. High-dose IL-2 would be the dose of choice. The majority of the trials of high-dose single-agent IL-2 for metastatic melanoma (6,11,13,14,16) used a dose of 600,000 IU/kg/dose and the United States Food and Drug Administration approved that same dose for the treatment of patients with metastatic melanoma. Guidelines for the safe administration of high-dose IL-2 published by the Surgery Branch, National Cancer Institute, National Institutes of Health recommend a dose and schedule of 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, to a maximum of 14 doses (29).

Patients receiving IL-2 treatment may experience gastrointestinal, cardiovascular, pulmonary, renal, hepatic, septic and neurologic toxicity. Most of the trials identified in this systematic review reported that the majority of these adverse events were readily resolved upon termination of treatment. In addition, when IL-2 is administrated in appropriately selected patients, in an expert setting, the incidence of toxic death is rare (1-6%). Improved initial screening practices, enhanced patient monitoring along with growing expertise has resulted in significant decreases in treatment-mortality over the years. Kammula et al (30) reviewed the safety of administration of high dose IL-2 in a consecutive series of 1241 cancer patients treated over a 12 year period (1985 –1997) at the NCI Surgery Branch. Interestingly,

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the study reported significant decreases in grade 3-4 toxicities over the years and more importantly there were no treatment related deaths in the last 809 patients reviewed (30).

The National Cancer Institute guidelines for the safe administration of high-dose IL-2 (29) provide guidance for pre-therapy assessment and intervention, patient monitoring during therapy, intervention during therapy and post-therapy assessment and intervention. It should be emphasized that IL-2 should only be administered by experienced clinicians in a centre with appropriate training and experience. Safety has not been established in patients with unresected brain metastases, or cardiac, renal, pulmonary, or hepatic dysfunction. Such patients should not be treated with high-dose IL-2 as part of a standard protocol.

Quality of life has not been assessed in patients receiving high dose IL-2. However, one randomized trial of low-dose single-agent IL-2 compared to low-dose IL-2 plus HD reported that median quality-adjusted survival was significantly longer for patients receiving the combination treatment (24). For patients with liver metastases, those that received IL-2 + HD had significantly longer median quality-adjusted survival and significantly less decline in QOL (measured by the QWB-SA questionnaire) over time than patients that received single-agent IL-2.

In summary, metastatic melanoma has a dismal prognosis for which our standard of care is the palliation of symptoms. At first glance, trials of high-dose IL-2 reported objective response rates similar to conventional chemotherapy. Data from three randomized controlled trials has demonstrated that single-agent IL-2, when given in high doses, can elicit an objective response rate of 5% to 27% with complete responses in 0% to 4% of patients (6,7,8). Similarly several noncomparative phase II trials of high-dose single-agent IL-2 have reported objective response rates of 10% to 33% with complete responses ranging from 0% to 15% (11-19). Complete responders in phase II trials have also demonstrated impressive long-term responses that range from 1.5 to 148 months (median 70 months). Though it has substantial toxicity, new guidelines and experience have made treatment with IL-2 manageable. The adverse effects are self-limiting and disappear shortly after completion of therapy. Given the data, it is possible to select appropriate patients for high-dose IL-2 that would have the greatest probability of response.

The studies which address prognostic factors suggest that it would be optimal to use IL-2 as first line therapy when disease burden is at its lowest. In this select group of patients, this therapy may be of potential value and should be considered as an option. However, given that some aspects of high dose IL-2 therapy remain investigational, and that response rates are low, patients should also be considered for clinical trials. Large randomized studies comparing IL-2 to DTIC or other chemotherapy are unlikely to be conducted in the future, as IL-2 is widely used in the United States and is an approved therapy in both Canada and the U.S.

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 of single-agent IL-2 in the treatment of patients with metastatic melanoma.

Protocol ID	**Title and details of trial**
CCCGHS-NCI-T98-0085, NCI-99-C-0051B, NCI-T98-0085	Phase III Randomized Study of High-Dose Interleukin-2 With or Without gp100 Antigen in Patients With Locally Advanced or Metastatic Cutaneous Melanoma. Target accrual: 93-185. Outcomes: Response, toxicity, progression-free and disease-free survival, quality-of-life. Date last modified: 11/5/2004. Accessed: March 12, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=66963&version=HealthProfessional&protocolsearchid=1492777

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CONCLUSIONS

Data from randomized trials as well as data from single-arm phase II trials of single-agent IL-2 demonstrate that IL-2 given in high doses can elicit an objective response rate of 5% to 33%. The randomized trials demonstrate that in the 0% to 11% of patients, who are complete responders, there have been consistent observations of long-term responses that range from 6 to 66+ months. Therefore, offering high-dose IL-2 to a select group of patients with metastatic melanoma is reasonable. Patients that have a good performance status (ECOG 0 or 1) and a normal LDH level, as well as having less than 3 organs involved or cutaneous and/or subcutaneous metastases only may benefit from treatment with high-dose IL-2. This carefully selected group of patients should be considered for treatment with high-dose IL-2 as no other therapy for metastatic melanoma has shown consistent durable responses.

There are no RCTs that compare high-dose IL-2 with the current standard treatment for metastatic melanoma, DTIC. However, DTIC is used for palliation of symptoms and offers low response rates with no benefit in survival.

High-dose IL-2 should be administered at a dose and schedule of 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, for a maximum of 14 doses. This is the same dose that the majority of trials of high-dose single-agent IL-2 used as well as the same dose as recommended by the National Cancer Institute.

High-dose IL-2 is an extremely toxic therapy, and it should be delivered only in a tertiary care facility where patients will receive appropriate monitoring by staff trained in the provisions of this treatment. Toxicity is manageable with the use of available guidelines and trained staff.

CONFLICT OF INTEREST

Members of the Melanoma DSG disclosed information on potential conflicts of interest. No potential conflicts were declared.

JOURNAL REFERENCES

- Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a clinical practice guideline. Curr Oncol. 2007;14(1):21-6.
- Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev. 2007 Aug;33(5):484-496. Epub 2007 Jun 11. doi:10.1016/j.ctrv.2007.04.003.
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For a complete list of the Melanoma DSG members please visit the CCO Web site at http://www.cancercare.on.ca/

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REFERENCES

1. National Cancer Institute of Canada. Canadian Cancer Statistics 2004. Toronto, Canada; 2004.
2. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999;17(9):2745-51.
3. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18(1):158-66.
4. Millward MJ, Bedikian AY, Conry RM, Gore ME, Pehamberger HE, Sterry W, et al. Randomized multinational phase III trial of dacarbazine with or without BCL-2 antisense in patients with advanced malignant melanoma: analysis of long term survival. Proc Am Soc Clin Oncol. 2004;22:711s.
5. Allen IE, Kupelnick B, Kumashiro M, Luo D, Ross SD, Wolin MJ. Efficacy of interleukin-2 in the treatment of metastatic melanoma. Systematic review and meta-analysis. Cancer Ther. 1998;1(3):168-73.
6. Sparano JA, Fisher RI, Sunderland M, Margolin K, Ernest ML, Sznol M, et al. Randomized phase III trial of treatment with high-dose interleukin-2 either alone or in combination with interferon alfa-2a in patients with advanced melanoma. J Clin Oncol. 1993;11(10):1969-77.
7. Rosenberg SA, Lotze MT, Yang JC, Topalian SL, Chang AE, Schwartzentruber DJ, et al. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. J Natl Cancer Inst. 1993;85(8):622-32.
8. McCabe MS, Stablein D, Hawkins MJ. The modified group C experience - phase III randomized trials of IL-2 and IL-2/LAK in advanced renal cell carcinoma and advanced melanoma [abstract]. Proc Am Soc Clin Oncol. 1991;10:213. Abstract #714.
9. Agarwala SS, Glaspy J, O'Day SJ, Mitchell M, Gutheil J, Whitman E, et al. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. J Clin Oncol. 2002;20(1):125-33.
10. Richards JM, Bajorin DF, Vogelzang NJ, Houghton AN, Seigler HF, Sell K, et al. Treatment of metastatic melanoma with continuous intravenous (CIV) IL-2 +/- LAK cells: a randomized trial [abstract]. Proc Am Soc Clin Oncol. 1990;9:A1080.
11. Agarwala SS, Tarhini A, Gooding W, Cai C, Kirkwood JM, Stover LL. Phase II trial of high-dose bolus (HDB) IL-2 in patients with metastatic melanoma (MM) who have progressed after biochemotherapy (BCT)- Updated Results. [abstract]. J Clin Oncol. 2005;23(16 Suppl):A7548.
12. Pappo I, Lotem M, Klein M, Orda R. Bolus high dose interleukin-2 for the treatment of malignant melanoma. Isr Med Assoc J. 2001;3(3):169-73.
13. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17(7):2105-16.
14. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am. 2000;6 Suppl 1:S11-4.
15. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. Ann Surg. 1998;228(3):307-19.

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16. Whitehead RP, Kopecky KJ, Samson MK, Costanzi JJ, Natale RB, Feun LG, et al. Phase II study of intravenous bolus recombinant interleukin-2 in advanced malignant melanoma: Southwest Oncology Group study. J Natl Cancer Inst. 1991;83(17):1250-2.
17. Parkinson DR, Abrams JS, Wiernik PH, Rayner AA, Margolin KA, Van Echo DA, et al. Interleukin-2 therapy in patients with metastatic malignant melanoma: a phase II study. J Clin Oncol. 1990;8(10):1650-6.
18. Rosenberg SA, Lotze MT, Yang JC, Aebersold PM, Linehan WM, Seipp CA, et al. Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. Ann Surg. 1989;210(4):474-84.
19. Thatcher N, Dazzi H, Johnson RJ, Russell S, Ghosh AK, Moore M, et al. Recombinant interleukin-2 (rIL-2) given intrasplenically and intravenously for advanced malignant melanoma. A phase I and II study. Br J Cancer. 1989;60(5):770-4.
20. Legha SS, Gianan MA, Plager C, Eton OE, Papadopoulous NE. Evaluation of interleukin-2 administered by continuous infusion in patients with metastatic melanoma. Cancer. 1996;77(1):89-96.
21. Vlasveld LT, Horenblas S, Hekman A, Hilton AM, Dubbelman AC, Melief CJ, et al. Phase II study of intermittent continuous infusion of low-dose recombinant interleukin-2 in advanced melanoma and renal cell cancer. Ann Oncol. 1994;5(2):179-81.
22. Dorval T, Mathiot C, Chosidow O, Revuz J, Avril MF, Guillaume JC, et al. IL-2 phase II trial in metastatic melanoma: analysis of clinical and immunological parameters. Biotechnol Ther. 1992;3(1-2):63-79.
23. Paciucci PA. Immunotherapy of metastatic melanoma with interleukin-2. Mt Sinai J Med. 1992;59(3):238-43.
24. Beusterien KM, Ackerman SJ, Plante K, Glaspy J, Naredi P, Wood D, et al. The health-related quality-of-life impact of histamine dihydrochloride plus interleukin-2 compared with interleukin-2 alone in patients with metastatic melanoma. Support Care Cancer. 2003;11(5):304-12.
25. Keilholz U, Conradt C, Legha SS, Khayat D, Scheibenbogen C, Thatcher N, et al. Results of interleukin-2-based treatment in advanced melanoma: a case record-based analysis of 631 patients. J Clin Oncol. 1998;16(9):2921-9.
26. Balch CM, Buzaid AC, Soong S-J, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer Staging system for cutaneous melanoma. J Clin Oncol. 2001;19(16):3635-48.
27. Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors associated with response to high-dose interleukin-2 in patients with metastatic melanoma. J Clin Oncol. 2001;19(15):3477-82.
28. Weinreich DM, Rosenberg SA. Response rates of patients with metastatic melanoma to high-dose intravenous interleukin-2 after prior exposure to alpha-interferon or low-dose interleukin-2. J Immunother. 2002;25(2):185-7.
29. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. J Immunother. 2001;24(4):287-93.
30. Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer. 1998;83(4):797-805.

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Evidence-based Series #8-5: Section 3

Single-Agent Interleukin-2 in the Treatment of Metastatic Melanoma: Guideline Development and External Review: Methods and Results

T. Petrella, I. Quirt, S. Verma, A. Haynes, M. Charette, K. Bak, and members of the Melanoma Disease Site Group

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

Please see the EBS 8-5 Version 2 Guideline Review Summary and the Document Assessment & Review Tool for the summary of updated evidence published between 2006 and 2010.

Report Date: March 20, 2006

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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, 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 clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Melanoma DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on single-agent interleukin-2 (IL-2) for patients with metastatic melanoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group Consensus Process

The guideline was circulated for review and discussion by the Melanoma DSG on June 21, 2005. Most of the members conceded that given the available data, it would be optimal to use IL-2 as first line therapy in a select group of patients when disease burden is at its lowest. However, it should be noted that one member of the Melanoma DSG was not comfortable with the recommendations set out in this document, stating that IL-2 "is and remains an investigational drug" and thus should not be used as standard therapy.

External Review by Ontario Clinicians

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

BOX 1:
RECOMMENDATIONS (approved for external review July 8, 2005)

Target Population

- Patients should have a good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1), and a normal lactate dehydrogenase (LDH) level.
- Patients should have less than three organs involved or have cutaneous and/or subcutaneous metastases only.

Recommendations

There is no high quality randomized controlled trial evidence to support or refute the use of interleukin-2 (IL-2) for patients with metastatic melanoma, and there are no studies that compare IL-2 to the current standard of care, dacarbazine (DTIC), or to placebo.

- After weighing and reviewing the evidence that does exist, the opinion of the Melanoma Disease Site Group is that high-dose IL-2 is a reasonable treatment option for a select group of patients with metastatic melanoma:

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- The recommended dose and schedule of high-dose IL-2 is 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, for a maximum of 14 doses.
- If high-dose IL-2 is delivered, the recommendation is that it be done in a tertiary care facility with staff trained in the provision of this treatment with appropriate monitoring.
- To facilitate patient treatment and develop expertise in this therapeutic modality, the recommendation is that high-dose IL-2 programs be established in one or two centres in Ontario.

Methods

Feedback was obtained through a mailed survey of 276 practitioners in Ontario (medical oncologists, radiation oncologists and surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the recommendations and whether the recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on July 8, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma DSG reviewed the results of the survey.

Results

Sixty-five responses were received out of the 176 surveys sent (37% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 29 (45%) 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 9.

Table 9. Responses to eight items on the practitioner feedback survey.

Item	Number (%)* Number			
	Rated "strongly agree" or "agree"	**Rated "neither agree nor disagree"**	**Rated "disagree" or "disagree strongly"**	**No answer**
The rationale for developing a guideline, as stated in the "*Introduction*" section of the draft report, is clear.	27 (93%)	1 (3%)	0	1 (3%)
There is a need for a guideline on this topic.	27 (93%)	0	2 (7%)	0
The literature search is relevant and complete (i.e., no key trials were missed nor any included that should not have been).	21 (72%)	8 (28%)	0	0
The results of the trials described in the draft report are interpreted according to my understanding of the data.	26 (90%)	1 (3%)	1 (3%)	1(3%)
The draft recommendations in the report are clear.	29 (100%)	0	0	0
I agree with the draft recommendations as stated.	26 (90%)	1 (3%)	2 (7%)	0
This report should be approved as a practice guideline.	24 (82%)	2 (7%)	2 (7%)	1 (3%)
	Rated "likely" or "very likely"	**Rated "unsure"**	**Rated "not at all likely" or "unlikely"**	**No answer**
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	21 (76%)	5 (10%)	2 (10%)	1 (3%)

† 5 (17%) practitioners indicated NA= not applicable for item #18 and 3 (10%) practitioners indicated NA= not applicable for item #19.

*For some items, percentages may not total 100 due to rounding error.

Education and Information

Summary of Written Comments

Twenty-two respondents (76%) provided written comments. The main points contained in the written comments were:

1. Two practitioners felt that there is insufficient evidence to recommend the use of IL-2 over other less toxic drugs. One of the two practitioners stated that the evidence of benefit is overstated and pointed out that in several studies the toxic death rate approximates complete response rates. Also pointing out that the guideline does not indicate "how to select eligible patients or what evidence supports selection (ie. no prospective studies showing selected patients do better)." A third practitioner also agreed that only a limited group would benefit and that it would be difficult to determine those fit enough to withstand the treatment.
2. Six respondents provided favourable comments and supported the guideline recommendations. Two of the six practitioners felt that administering IL-2 in Ontario is a more economically feasible option than sending patients to the United States. One respondent felt it would be practical to treat complete responders, however the challenge in establishment wait lists for these patients and centres to treat them in along with other associated financial costs will limit the application of these guidelines. It was also suggested that issues such as the cost of medicine, hospital visits and treatment of complications should be addressed.
3. Nine practitioners stated that they do not treat melanoma and/or that the guideline does not apply to them.
4. Six practitioners provided suggestions for future topics.

Modifications/Actions

The Melanoma DSG discussed the comments resulting from practitioner feedback and produced the following responses:

1. The DSG acknowledges that currently there is a lack of high quality evidence suggesting a clear survival benefit for IL-2 therapy. However, given the dismal survival of patients with metastatic melanoma and the fact that no other therapy offers the possibility for a durable complete remission the group believes that it is reasonable to recommend the use of high dose IL-2 to a select group of patients. The specific patient eligibility for this treatment is defined in Section 1 (page 2), Section 2 (pages 18 and 20), Section 3 (page 2) of the document. The group also agrees that high-dose IL-2 therapy presents considerable grade 3/4 toxicity; however; these adverse effects have become increasingly manageable. Delivering the treatment by adequately trained professionals in a designated tertiary care facility as well as following the National Cancer Institute's guidelines for safe administration will insure safety and proper patient monitoring. The DSG has decided not to make any changes to the guideline.
2. The Melanoma group agrees that administering IL-2 therapy in Ontario, rather than referring patients for this treatment to the United States, is a more economically feasible option. Creating high-dose IL-2 programs in one or two centres in Ontario will not only facilitate patient treatment but also develop expertise in this therapeutic modality. The group recognizes the importance of financial concerns brought up by some of the respondents; however, the DSG's main obligation is to establish clinical effect and determine best evidence-based practice, thus, assessing issues of cost and/or economic benefit is outside of the purview of this document.

Education and Information

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the PEBC Report Approval Panel in May, 2006. The Panel consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included:

1. The RCTs address all of the relevant outcomes although the data from the phase II trials are more favourable. Inclusion of the phase II data may be viewed as biased; therefore, clearer justification for the inclusion of the phase II data should be provided.
2. Where data is summarized (e.g. in the Key Evidence section), the RCT data should be included along with the phase II data. For example, complete response rates with high-dose IL-2 range from 0%.
3. Further discussion of the trade-offs of the treatment would be useful. The treatment may offer the best palliation option; however, it can lead to a miserable death with adverse effects for a slim chance of survival with unknown QOL because there are no appropriate comparisons.
4. It appears that access to this treatment is a topical subject, although the background for this only becomes apparent in the Practitioner Feedback section. If access to therapy was a contributing factor that led to the DSG selecting this topic, it would be appropriate to state this in the Introduction section.
5. The recommendations are principally based on studies that provide a lower level of evidence and principally assess an outcome that does not usually drive policy decisions. The DSG has done a relatively good job of explaining how it concluded that a recommendation to support availability of this therapy was appropriate. However, given the relatively unusual nature of recommending a therapy based on such data, and given the toxicity of the agent that may require development of special sites of provincial expertise, I think the DSG needs to go further to address how the potential benefits of this therapy "outweigh" the limitations of the data. Specifically:

   i) context regarding the importance of response as an outcome measure would be helpful.

   ii) an indication of whether the prolonged periods of disease control seen in CR patients is unique, or whether this is seen in patients who respond to other therapies, would be helpful. There is a further risk of criticism that the DSG has compared overall responses to IL-2 with the historical results associated with other therapies, but is only providing the data for durable responses with IL-2.

   iii) the DSG also risks criticism for its last sentence in the Discussion (p 19) that suggests that IL-2 might be considered as first - line therapy. This consideration appears to be principally based on analyses of prognostic factors. The difficulty is that patients with earlier stages of disease will always do better than those with more advanced disease, regardless of the therapy provided. More background is required to support this supposition.
6. The DSG also should consider providing broader context of the Agarwala study. This RCT was the largest of those reported, and described differences in median time to disease progression (likely a more "policy – determining" outcome than response) and median quality – adjusted survival. While the potential limitations of these data can be appreciated, an explanation of the reasons for not using the results of this trial to form recommendations when trials that have more severe limitations have been used would be helpful.

Education and Information

Modifications/Actions

The Melanoma DSG discussed the comments resulting from the PEBC Report Approval Panel and produced the following responses and modifications:

1. The DSG felt that the inclusion of phase II data was necessary due to the limited availability of phase III data. In order to further justify the inclusion of phase II data a Qualifying Statement has been added to Section One of the document.
2. The Key Evidence section has been modified to reflect these suggestions.
3. The working group would like to point out that IL-2 is not a palliative treatment. IL-2 offers similar response rates to the current standard of care, DTIC, adverse events are manageable and reversible and death due to treatment in no longer common.
4. Access to therapy was not a contributing factor that lead to the DSG's selection of this topic. The purpose of this document is to establish clinical effect and determine best evidence-based practice. However, the DSG would like to point out that access to treatment is addressed in the document (Discussion section).
5. The discussion section has been expanded to further address the benefits of IL-2 therapy and Qualifying Statements have been added to explain the DSG's decision to recommend IL-2 as first line therapy.
6. The DSG decided not to use the results of the Agarwala trial to form its recommendations because the trial randomized its patients to treatment with low-dose IL-2. Low dose IL-2 had consistently lower overall response rates (2 to 5%) compared to high dose IL-2 and hence was not part of the recommendation.

Policy Review

A draft of this evidence series was submitted to the Drug Quality and Therapeutics Committee/Cancer Care Ontario (DQTC/CCO) Subcommittee in 2005.

Education and Information

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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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

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REFERENCES

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.

Education and Information

EBS 8-5 Document Assessment and Review Tool.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	EBS #8-5 Single-Agent Interleukin-2 In The Treatment Of Metastatic Melanoma
Date of current version	March 20, 2006
Clinical reviewer	Dr. Teresa Petrella
Research coordinator	Rovena Tey
Date initiated	June 10, 2010
Date and final results / outcomes	**August 4, 2010 (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:	1. YES • This guideline is needed by the University Health Network (UHN) and Ministry of Health (MOH) to create an Ontario-based Interleukin-2 treatment program If No, then the document should be **ARCHIVED**1 with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. Definitive or Sufficient • YES, the current recommendations are probably definitive and sufficient, however, an updated literature search should still be conducted to see what new evidence might turn up • There may be new studies on molecular markers, which would be useful to answer Guideline Q2 about selecting patients for treatment. <5 y elapsed • YES If Yes, the document can be **ENDORSED**2 with no further action; **go to 11**. If No, **go to 3**.
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:	3. NO If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] 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, g**o to 4**.
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:	4. YES • There is a designated research co-ordinator at the PEBC to carry out the literature search • Updated literature search to be completed by mid-July 2010 If No, a **DEFERRAL**[3] 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**.

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).

- No changes to the original questions

Original Questions:

1. What is the role of single-agent interleukin-2 (IL-2) in the treatment of adults with metastatic melanoma? Primary outcomes of interest include objective response rates, complete response rates, duration of response, toxicity, and quality of life. Secondary outcomes of interest include progression-free survival and overall survival.
2. If there is a role for single-agent IL-2, what is the appropriate patient population to be considered for treatment?
3. If there is a role for single-agent IL-2, what is the appropriate dose and schedule?
4. What are the toxicities associated with IL-2?

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).

- No changes to the inclusion or exclusion criteria
- It is still important to include both RCTs and non-randomized phase II studies because it is still unlikely that there would be many randomized studies on this topic, especially to answer Guideline Q2 about patient populations

Inclusion Criteria:
The following types of articles were selected for inclusion in this systematic review of the evidence:

1. Full reports or abstracts of randomized controlled trials or randomized phase II trials in which one trial arm involved single-agent IL-2 for patients with metastatic melanoma.
2. Full reports or abstracts of single-arm phase II trials of single-agent IL-2 for patients with metastatic melanoma, which were included because insufficient evidence was available from randomized controlled trials.
3. Meta-analyses of randomized controlled trials, systematic reviews and evidence-based practice guidelines.

Exclusion Criteria:

1. Papers published in a language other than English were not considered due to limited resources for translation.
2. Phase I studies were not considered.
3. Reports that provided data for a sample of less than 10 patients with metastatic melanoma were 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:

The following types of articles were selected for inclusion in this systematic review of the evidence:

Education and Information

1. Full reports or abstracts of randomized controlled trials or randomized phase II trials in which one trial arm involved single-agent IL-2 for patients with metastatic melanoma.

2. Full reports or abstracts of single-arm phase II trials of single-agent IL-2 for patients with metastatic melanoma, which were included because insufficient evidence was available from randomized controlled trials.

3. Meta-analyses of randomized controlled trials, systematic reviews and evidence-based practice guidelines.

Exclusion Criteria:

1. Papers published in a language other than English were not considered due to limited resources for translation.

2. Phase I studies were not considered.

3. Reports that provided data for a sample of less than 10 patients with metastatic melanoma were excluded.

Search Period:

- March 2006 to 18th June 2010 (Medline + Embase)
- 2006 to 2010 (ASCO Annual Meeting)

Brief Summary/Discussion of New Evidence:
Of 530 total hits from the Medline + Embase search and looking through 519 ASCO conference abstracts, 8 references representing 8 potentially new studies were found evaluating high-dose IL2 in metastatic melanoma, of which there was 1 RCT. 2 were full text publications and 6 were abstracts.

The **BOLD** text within the table (last 3 rows) represent evidence that might help answer research Q2 regarding the selection of patients to be considered for IL2 treatment.

Interventions	Study type	Population	Outcomes	Brief results	References
High-dose IL2 (720 000 IU/kg) ***vs.*** peptide vaccine + high-dose IL2	Ph 3 RCT	Stg 4 metastatic or stg 3 locally advanced cutaneous melanoma	1 = response 2 = CR, PR, PFS, OS, toxicity	For IL2 vs. vaccine + IL2: • Response = 9.7% vs. 22% (P=0.02) • CR =2.2% vs. 14% (P=0.003) • PR = grps did not differ • PFS = 1.6 mo vs. 2.9 mo (P=0.01) • Median OS = grps did not differ • The IL2 + vaccine grp had more cardiovascular arrhythmias	(Schwartzentruber DJ et al. 2009) *[abstract]*
High-dose IL2 (600 000 to 720 000 U/kg/8h)	Ph 2 single-arm non-RCT	Stg 4 metastatic melanoma, previously treated with biochemotherapy (cisplatin, vinblastine, dacarbazine, IL2, IFNa-2b)	ORR, survival, PFS, toxicity	• ORR = 19% • median survival time at 10 mo = 42 wks (CI 19 to 87) • median PFS at 10 mo = 10 wks (CI 8 to 16) • Grd 3/4 toxicity included hyperbilirubinemia, thrombocytopenia, oliguria	(Tarhini AA et al. 2007)
High-dose IL2 (600 000 to 720 000 U/kg/8h)	Single-arm study	Metastatic melanoma	OS, PFS, response	• Median OS = 1.94 y • Median PFS = 57 d • Response = 30%	(Joseph RW et al. 2010) *[abstract]*
High-dose IL2 (600 000 IU/kg/8h)	Retrospective	Metastatic melanoma, previously treated with biochemotherapy (cisplatin, vinblastine, dacarbazine, INFa, IL2)	CR, PR, TTP, OS	• CR = 5% (n=1) • PR = 27% • DoR range = 1 to 18 mo • DFS = no survivors • Median TTP at 36 mo = 2.5 mo • Median OS at 36 mo = 9.5 mo	(Schmerling RA et al. 2006) *[abstract]*

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High-dose IL2 (600 000 IU/kg)	Retrospective	Stg 4 metastatic melanoma	CR, PR, TTP, toxicity	• CR = 6.7% (n=1) • PR = 6.7% (n=1) • TTP = 5.7 mo • Grd 3/4 toxicity included hyperbilirubinemia, hypotension, peripheral edema, pulmonary edema	(Powell SF et al. 2009) *[abstract]*
High-dose IL2	Single-arm study and retrospective clinical prediction study (no validation set)	Advanced melanoma	Response, CR, PR, OS, PFS, **predictive gene expression signature to treatment response**	• Response = 33% • CR = 8% • PR = 25% • Median OS = 24 mo • Median PFS = 3.3 mo • **Tumours expressing immune genes were more likely to respond to treatment compared with tumours expressing melanocyte genes**	(Sullivan RJ et al. 2009) *[abstract]*
High-dose IL2 (600 000 U/kg/8h)	Clinical prediction study (training and validation sets)	Mix of pts with metastatic melanoma (n=48) and renal cell carcinoma (n = 11)	CR, PR, toxicity, **predictive biomarkers of treatment response**	• In pts with melanoma, 37% achieved a response (10% CR + 27% PR) • There were no serious adverse events or treatment-related mortality • **High levels of serum VEGF and fibronectin correlated with lack of clinical response and decreased OS**	(Sabatino M et al. 2009)
High-dose IL2	Retrospective clinical prediction study	Metastatic melanoma	**Predictive hemodynamic parameters to treatment response**	• **Greater decrease in corrected mean BP at baseline, lower corrected mean BP during treatment, and decreases in corrected systolic and diastolic BP were associated with a response to treatment** • **No correlation was found between heart rate or number of IL2 doses and treatment response**	(Dutcher JP et al. 2006) *[abstract]*

BP = blood pressure; CI = confidence interval (95%); CR = complete response; DFS = disease-free survival; DoR = duration of response; IL = interleukin; IFN = interferon; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; RCT = randomized controlled trial; TTP = time to progression; VEGF = vascular endothelial growth factor; 1 = primary endpoint; 2 = secondary endpoint

New References Identified (alphabetical order):

Dutcher JP, Dasanu C, Codreanu I, et al. (2006) Correlation between hemodynamic parameters and response to high-dose interleukin-2 in metastatic melanoma. ASCO Meeting Abstracts 24(18 Suppl): 18012.

Joseph RW, Sullivan RJ, Panka D, et al. (2010) Effect of mutational status on response, PFS, or OS after treatment with IL-2 for metastatic melanoma. ASCO Meeting Abstracts 28(15 Suppl): 8597.

Powell SF and Dudek AZ (2009) Response to high-dose interleukin-2 (HD IL-2) therapy in patients with brain metastases from metastatic melanoma. ASCO Meeting Abstracts 27(15S): e20007.

Sabatino M, Kim-Schulze S, Panelli MC, et al. (2009) Serum vascular endothelial growth factor and fibronectin predict clinical response to high-dose interleukin-2 therapy. Journal of Clinical Oncology 27(16): 2645-52.

Schmerling RA, William WN, Jr, Belfort FA, et al. (2006) High-dose IL-2 in patients with metastatic melanoma after progression on biochemotherapy (BioCT). The experience of the Hospital Sirio-Libanes, Brazil. ASCO Meeting Abstracts 24(18 Suppl): 8038.

Schwartzentruber DJ, Lawson D, Richards J, et al. (2009) A phase III multi-institutional randomized study of immunization with the gp100: 209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma. ASCO Meeting Abstracts 27(18S): CRA9011.

Education and Information

Sullivan RJ, Hoshida Y, Brunet J, et al. (2009) A single center experience with high-dose (HD) IL-2 treatment for patients with advanced melanoma and pilot investigation of a novel gene expression signature as a predictor of response. ASCO Meeting Abstracts 27(15S): 9003.

Tarhini AA, Kirkwood JM, Gooding WE, et al. (2007) Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy. Journal of Clinical Oncology 25(25): 3802-7.

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$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp melanoma/
39. melanoma.mp.
40. 38 or 39
41. interleukin-2/ or IL-2/
42. (interleukin 2 or interleukin-2 or IL-2 or IL 2).mp.
43. 41 or 42
44. 40 and 43
45. 37 and 44
46. (200603$ or 2007$ or 2008$ or 2009$ or 2010$).ed.
47. 45 and 46

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 synthes?s 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)

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9. or/1-4,8
10. (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.
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$3 or dummy)).tw.
19. placebo/
20. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
21. (allocated adj2 random).tw.
22. or/17-21
23. practice guidelines/
24. practice guideline?.tw.
25. practice guideline.pt.
26. or/23-25
27. 9 or 10 or 11 or 15 or 16 or 22 or 26
28. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
29. 27 not 28
30. limit 29 to english
31. limit 30 to human
32. exp melanoma/
33. melanoma.mp.
34. 32 or 33
35. interleukin-2/ or IL-2/
36. (interleukin 2 or interleukin-2 or IL-2 or IL 2).mp.
37. 35 or 36
38. 34 and 37
39. 31 and 38
40. (200615$ or 2007$ or 2008$ or 2009$ or 2010$).ew.
41. 39 and 40

ASCO Annual Meeting – manually checked all abstracts from www.asco.org in the section: Melanoma/Skin Cancers (2006 to 2010)

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:	7. YES • No new recommendations are needed as the studies addressing patient populations are retrospective or single arm studies and would require prospective validation in larger data sets prior to being incorporated into clinical practice • The rest of the data does not change our current recommendations • Therefore, Guideline 8-5 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 website, 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 website. Notify the original authors of the document about this review.	
DSG Approval Date:	**August 4, 2010**

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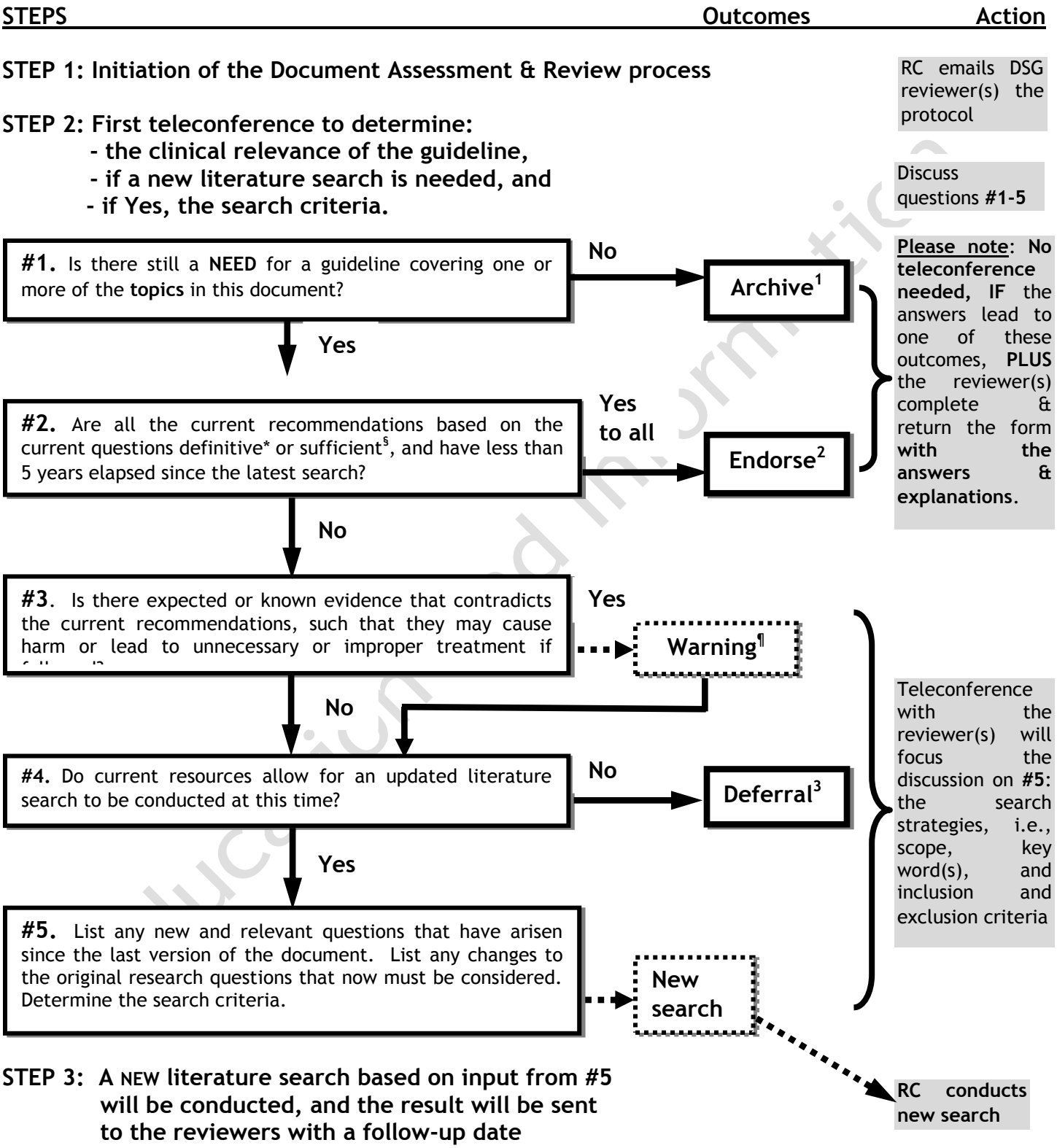
DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)

STEPS **Outcomes** **Action**

STEP 4: Second teleconference to determine the ultimate status of the document

Review questions **#6-9**

#6. Are the volume and content of the newly identified evidence such that **a new document is necessary** to address the topic?

Yes → **Archive**

No

#7. 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?

Yes to all → **Endorse**

No

#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?

Yes → **Warning**

No

#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?

Yes → **Deferral**

No

#10. An update should be initiated as soon as possible. List the expected date of completion of the update.

Yes → **Update**[4]

Please note: **No teleconference needed**, **IF** the reviewer(s) complete and return the form **with answers & explanations.**

Teleconference with the reviewer(s) to discuss the **type of update, priority, and resources.**

STEP 5: Final outcome approval; Document Assessment & Review questions #11

#11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

RC emails draft for DSG approval

Educational Information

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 website, 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 our Web site, **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 due to a number of reasons. The reasons for deferral should be found in the Document & Assessment Review form and on the document.

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.

Education and Information