ADJUVANT INTERFERON
FOR MALIGNANT MELANOMA

Effective Date: February 2014

The recommendations contained in this guideline are a consensus of the Alberta Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Despite advances in the staging and surgical therapy of melanoma, patients with high-risk resected melanoma still have 5-year recurrence rates of 55-80% and 5-year survival rates as low as 25-70%. This poor prognosis has prompted oncologists to search for an effective adjuvant therapy to be used after primary tumour resection or after dissection of regional lymph node metastases. 1

The concept of adjuvant therapy for melanoma is based on the hypothesis that these therapies may have an effect on micrometastatic disease that is the source for future relapse. Systemic adjuvant treatment of melanoma may be considered when a patient is clinically free of disease following surgical excision of the primary high-risk tumor and possibly one or more positive regional lymph nodes and is at high risk for recurrence.

Interferons are a group of naturally occurring proteins with a large spectrum of biologic activities including antiviral, immunomodulatory, antiproliferative, and differentiation-inducing effects. 1-4 Treatment with interferon alfa has been shown to increase the 4-year disease-free survival rate in melanoma patients at moderate to high risk of developing metastatic disease after surgery by approximately 6.7% 5 and in some studies, to increase overall survival by as much as 12 months (from 27 to 39 months) in this patient population. 6-14

GUIDELINE QUESTIONS

Should adjuvant interferon alpha be offered to patients who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk for subsequent recurrence?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The MEDLINE (1966 through December 2010), CINAHL, Cochrane, ASCO Abstracts and proceedings, and CANCERLIT databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Search terms included: interferon or adjuvant interferon and malignant melanoma.

PubMed was again searched in 2013 for evidence on adjuvant interferon in cutaneous melanoma. The search term “melanoma” was used and results were limited to clinical trials, published between January 2012 and January 2013. Citations were hand-searched for studies pertaining to interferon therapy. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes to the recommendations were made.
Using the same search strategy, four relevant articles published between January 2013 and January 2014 were identified during the 2014 update. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes were made to the recommendations.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with malignant melanoma. Different principles may apply to pediatric patients.

RECOMMENDATIONS

These recommendations were adapted from: Management of Malignant Melanoma: Best Practices, 2006 (Canadian Expert Panel on Malignant Melanoma).

- Enrollment in a clinical trial should be encouraged/considered.
- Most patients with in-situ or early-stage melanoma will be cured by primary excision alone. Therefore, no standard adjuvant therapy is recommended for patients with melanoma that is in-situ, less than 2 mm thick, 2-4 mm thick but non-ulcerated or node-negative.
- Patients with primary tumors that are 2.01-4.0 mm thick and ulcerated, deep primary tumors (T4), primary tumor of any thickness with positive sentinel nodes or resected overt nodal disease, including patients who relapse in the nodal basin, should be referred to medical oncology for consideration for adjuvant therapy.

<table>
<thead>
<tr>
<th>Features of High Risk</th>
<th>15,16</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary melanoma with tumour thickness ≥4.0 mm or Clark level V invasion</td>
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<tr>
<td>primary melanoma with in-transit metastases</td>
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<tr>
<td>primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph-node dissection</td>
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<tr>
<td>regional lymph node recurrence</td>
<td></td>
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<tr>
<td>involved nodes were excised but there was no known primary melanoma</td>
<td></td>
</tr>
<tr>
<td>primary melanoma with tumour thickness 2.01-4.0 mm with ulceration</td>
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</tr>
</tbody>
</table>

- Patients who are at high-risk for disease recurrence following complete surgical resection of the primary tumor are eligible for adjuvant treatment with interferon-alfa.
- Prior to the initiation of treatment rule out metastatic disease:
  - Refer to staging guidelines 17 (Appendix)
- Contraindications to interferon are:
  - a history of hypersensitivity to IFNa
  - active cardiovascular disease (myocardial infarction within 6 months, active angina, or dysrhythmias)
  - pre-existing liver disease
  - central nervous system disease
- serious psychiatric conditions (including major depression)
- active autoimmune disease
- any debilitating medical condition is a relative contraindication because of the toxicities expected.

- Before initiating high-dose adjuvant interferon therapy, the following baseline laboratory tests are required: 5,15
  - CBC/differential
  - Hemoglobin
  - Hematocrit
  - Platelets
  - blood chemistry including electrolytes
  - liver function tests (ALT/AST)
  - TSH
  - Additional testing, such as CPK if abnormal troponin level, anti-thyroid antibodies and anti-nuclear antibodies, may be required

Treatment

- Pre-medication: Acetaminophen 650 mg PO 30 minutes pre- IV Interferon-α and every 4-6 hours regularly during induction phase

- Induction phase: 20 MU/m² intravenously 5 days per week for 4 weeks
  - Depending on the patient's performance status and symptoms, a rest period of 2 weeks between induction phase (weeks 1-4) and maintenance phase (weeks 5-52) may be considered. 18

- Maintenance phase: 10 MU/m² subcutaneously three times per week for 48 weeks.

- Laboratory tests should be performed weekly during induction phase and monthly during maintenance phase: 18
  - CBC and differential, platelets, LFTs
  - Assessment for mood changes during clinic visits

Side Effects

- Fever, chills and rigors often occur when interferon therapy is first initiated but diminish over time.

- Treatment with interferon-alfa is associated with a significant number of side effects that require close monitoring. 19-21 These side-effects may hamper reaching and maintaining the dose needed for maximal therapeutic effect. 22
  - Common side effects are fatigue, fever, myalgia, anorexia, nausea, headache and chills (“flu-like” symptoms).
  - The incidence of severe neuropsychiatric disorders, such as depression, can be as high as 10% so close monitoring is recommended. Referral to a psychiatrist may be required.
  - The following are recommended to alleviate side effects:
− Regular exercise to relieve fatigue
− Due to fluid losses through increased heart and metabolic rates, fever and sweats, an aggressive fluid hydration strategy is recommended. Administer 500 mL IV normal saline before each IV infusion. A daily oral intake of >2 litres of fluids, especially water, throughout therapy is advised. Avoid caffeine and alcohol containing beverages as they can cause dehydration.
− Acetaminophen before each injection and/or at bedtime; consider another antipyretic/anti-inflammatory if acetaminophen is not effective
− Headaches are common. Tension-type headaches may require mild opioids. Migraine-like headaches may require treatment as for migraine
− Patients should be advised that side effects are worse on Mondays
− An anti-emetic (e.g. metoclopramide, prochlorperazine) may be required to relieve nausea; 5-HT3 antagonists can be helpful for chronic nausea
− Depression can be treated with antidepressants

- Long-term side effects that can result in dose alterations, disruptions and even discontinuation of therapy are: 23
  − Hepatotoxicity: Transient elevations in AST and ALT are common. Elevations more than five times the normal range require dose adjustment
  − If radiation is to be part of the regimen, interferon-alfa should not be given concurrently due to the risk of skin toxicity
  − Patients with psoriasis may experience a worsening of their condition. This may require a dermatology consult
  − Weight loss is common and patients may benefit from dietary counseling. If there is clinical concern, a dose reduction or cessation of therapy is indicated

- Potentially life-threatening side effects can occur but these are rare:
  ▪ In the event of serious side effects, the dose should be held until the medical oncologist is contacted
  ▪ If the ANC < 500 cells/mL or ALT/AST > 5-10 times normal, it is recommended that subsequent doses be held until the toxicity resolves re-initiation, which should be started at 50% of the previous interferon-alfa dose
  ▪ Therapy should be discontinued if the ANC < 250 cells/mL and/or ALT/AST >10 times normal
  ▪ Suicidal ideation has been reported and is a contraindication to further IFNa2b therapy 24

Special Considerations

- The successful administration of IFNa2b requires the services of a specialized and committed team of health care professionals, including physician, oncology nurse, social worker, pharmacist, and behavioral therapist or psychologist.
- Because hematologic and hepatic toxicity associated with HDI therapy can be severe, ongoing monitoring is essential to ensure safety. White blood cell counts and liver function tests should be performed weekly during induction and monthly during maintenance therapy for at least 3 months, and then at least every 3 months in patients who are stable with no new complaints.
- Patient education is vital to help understand and anticipate the nature of the side effects and the
interventions available to manage adverse events and preserve quality of life.

- During the maintenance phase, constitutional symptoms are managed by administering IFNa at bedtime with prophylactic antipyretics such as acetaminophen or ibuprofen.

- Meperidine may be useful for severe chills and rigors. Nausea and vomiting are uncommon but respond well to standard anti-emetics such as chlorpromazine or metoclopramide. Attention to fluid balance during IFNa therapy is critical. Because flu-like symptoms may cause dehydration, which tends to exacerbate other symptoms, proper hydration (≥ 2 L daily) must be ensured. Non-caffeinated fluids are preferred for oral and intravenous hydration (500-1000 mL daily) and may be used in selected patients. Antidepressants are effective in reducing fatigue and depression; prophylactic administration of these agents has been investigated. 25

Follow-Up

- These patients will be seen by the attending medical oncologist monthly during the year of treatment, every 3 months for 2 more years and then every 6 months thereafter in the outpatient clinic.

DISCUSSION

A recent meta-analysis of data from 18 randomized controlled trials among high-risk cutaneous melanoma patients (n=10,499) showed that IFN-alpha treatment was associated with a significant improvement in DFS (HR for disease recurrence 0.83; 95% CI 0.78-0.87; P<.00001) and OS (HR for death 0.91; 95% CI 0.85-0.97; P=.003); however, no optimal IFN-alpha dose and/or treatment duration or a subset of patients more responsive to adjuvant therapy was identified. 26,27 Among the trials comparing high dose with observation, 12,13,28-30 the combined disease free and overall survival hazard ratio estimates were 0.75 (95% CI 0.68-0.83) and 0.89 (95% CI 0.77-1.02), respectively. Among the trials comparing low- or intermediate-dose with observation, 14,31-37 the combined disease free and overall survival hazard ratio estimates were 0.85 (95% CI 0.78-0.93) and 0.89 (95% CI 0.81-0.98), respectively. 26 A subsequent study by Hauschild, et al. (2009) showed no differences between high-dose (IFNa-2b: 10 MU/m² IV 5 times per week for 2 weeks, followed by 10 MU/m² SC 5 times per week for 2 weeks, followed by 3 MU SC 3 times per week for 23 months) and low-dose (IFN-α-2b: 3 MU SC 3 times per week for 24 months) interferon, in terms of five-year relapse-free (68.0 vs. 67.1%, respectively) and overall (80.2 vs. 82.9%, respectively) survival. 38 Similar results were reported elsewhere. 39

The use of pegylated interferon has become an alternative option to high-dose interferon. The European Society for Medical Oncology guidelines (2010) 40 state that pegylated interferon can be recommended, if the individual patient tolerates it well. Likewise, Cancer Care Ontario guidelines (2009) 41 state that patients who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk of recurrence (AJCC stage IIIB/IIIC/III) could be considered for pegylated interferon (subcutaneous, 6 μg/kg per week for eight weeks followed by 3μg/kg per week for a duration of five years) as a reasonable alternative to high-dose interferon, provided that each patient has been made aware of the relative risks, benefits, and costs of this therapy and wishes to proceed. Data from a recent EORTC trial by Bottomley, et al. (2009) comparing adjuvant pegylated IFN-α2b (induction 6 MU/kg per week for 8 weeks, followed by 3 MU/kg per week for a total of five years) with observation with a median follow-up of 3.8 years showed that the risk of recurrence was reduced by 18% (HR 0.82; P=.01) with pegylated interferon. 42 A randomized phase III trial by the European Society for Dermato-Oncology...
(EADO) study comparing low-dose interferon (IFN) alfa-2b with pegylated interferon (Peg-IFN) alfa-2b among 898 patients with resected melanoma ≥1.5 mm thick and without clinically detectable node metastases found that after a median follow-up of 4.7 years, there were no statistical differences between the two arms for the primary outcome of DFS (HR 0.91, 95% CI 0.73-1.15) or the secondary outcomes of distant metastases-free survival (HR 1.02, 95% CI 0.80-1.32) and OS (HR 1.09, 95% CI 0.82-1.45). 43

Two trials have evaluated the effect of duration of interferon therapy on survival outcomes. Pectasides, et al. (2009) compared intravenous induction therapy alone (IFN-α2b 15 MU/m² 5 times per week for 4 weeks) with induction therapy plus 48 weeks of subcutaneous maintenance therapy (IFN-α2b 10 MU/m² 3 times per week for 48 weeks) and showed no differences in recurrence-free (24.1 vs. 27.9 months; P=.90) or overall (64.4 vs. 65.3 months; P=.49) survival at a median follow-up of 63 months. 44 In a long-term study comparing 18 months with 60 months of subcutaneous interferon (3 MU IFN-α2a 3 times per week), with median follow-up of 4.3 years, there were no differences in distant metastasis-free (75.6 vs. 72.6%, respectively; P=.72) or overall (85.9 vs. 84.9%, respectively; P=.86) survival. 45 In 2012, additional quality of life data from a randomized phase III trial became available. The Nordic trial compared IFN alfa-2b for 1 year (10 MU SC, 5 days per week for 4 wks plus maintenance therapy (10 MU SC, 3 days per week for 1 year) with IFN alfa-2b for 2 years and with observation among patients with resected stage IIb (T4 N0 M0) or stage III (Tx N1-3 M0) melanoma (N=855). Patients in the one-year treatment group demonstrated improvements in functioning and quality of life at 4 months post-treatment, as compared to 0 months post-treatment (p<0.001). 46 Role functioning was later found to be an independent prognostic factor for time to failure and survival in patients with high-risk melanoma. 47 Median recurrence-free survival was better in the one-year treatment group (37.8 months vs. 28.6 months). 48

The addition of chemotherapy to interferon has not been shown to further improve survival outcomes. 49,50 Maio, et al. (2010) compared several regimens of dacarbazine ± IFN-α ± thymosin-α in patients with metastatic melanoma and found no significant differences among the treatment groups in terms of overall response rate or overall survival at one year; however, progression-free survival at six months was significantly better with the dacarbazine-thymosin combination as compared with the dacarbazine-interferon combination (15.9 vs. 9.1%, respectively; P≤.05). 51 A randomized phase III trial among 260 patients compared four treatment groups: (A) fotemustine and dacarbazine repeated on 3-week cycle; (B) same treatment as (A) plus IFN-α2b three times per week; (C) dacarbazine alone repeated on 3-week cycle; (D) same treatment as (C) plus IFN-α2b three times per week. Addition of IFN-α2b did not improve OS (HR 0.92, 95% CI 0.70-1.20; p=0.68) or PFS (p=0.65). 52 Given the lack of data showing efficacy, the addition of chemotherapy to interferon is not supported.

**DISSEMINATION**

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

**MAINTENANCE**

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


## APPENDIX

### AJCC 2009 (7th Edition) Anatomic Stage Groupings for Cutaneous Melanoma

<table>
<thead>
<tr>
<th></th>
<th>Clinical Staging a</th>
<th>Pathologic Staging b</th>
<th>5-year Survival (%)</th>
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</thead>
<tbody>
<tr>
<td>T</td>
<td>N</td>
<td>M</td>
<td>T</td>
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<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
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<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
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<tr>
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<td>M0</td>
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<tr>
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<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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a Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

b Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
## AJCC 2009 (7th Edition) TNM Staging Categories for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>T</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
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<tr>
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<td>NA</td>
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<tr>
<td>T1</td>
<td>≤ 1.00</td>
<td>a: without ulceration and mitosis &lt; 1/mm²</td>
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<td></td>
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<td>b: with ulceration or mitoses ≥ 1/mm²</td>
</tr>
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<td>1.01-2.00</td>
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<td></td>
<td></td>
<td>b: with ulceration</td>
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<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH (lactate dehydrogenase)</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
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<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
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</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
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</table>

\(^a\) Micrometastases are diagnosed after sentinel lymph node biopsy.

\(^b\) Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.