

ADJUVANT INTERFERON FOR MALIGNANT MELANOMA

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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% to 80% and 5-year survival rates as low as 25% to 70%. This poor prognosis has prompted oncologists to search for an effective adjuvant therapy to be used after primary tumor 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.^{2,3,4,5} Treatment with interferon alfa has been shown to prolong disease-free survival in melanoma patients at moderate to high risk of developing metastatic disease after surgery¹⁴ and in some studies, to prolong overall survival in this patient population.^{6,7,8,9,10,11,12,13,14}

GUIDELINE GOALS AND OBJECTIVES

To improve overall survival, disease-free survival, and quality of life for adult patients with high-risk malignant melanoma who are rendered disease-free following resection.

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.

SEARCH STRATEGY

The MEDLINE (1966 through April 2009), 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.

RECOMMENDATIONS

These recommendations were adapted from: *Management of Malignant Melanoma: Best Practices, 2006* (Canadian Expert Panel on Malignant Melanoma)¹⁵

- 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.

Features of High Risk^{16,17}

- primary melanoma with tumour thickness ≥ 4.0 mm or Clark level V invasion
- primary melanoma with in-transit metastases
- primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph-node dissection
- regional lymph node recurrence
- involved nodes were excised but there was no known primary melanoma
- primary melanoma with tumour thickness 2.01-4.0 mm with ulceration.

- 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 (Appendix A)
- Contraindications to interferon are:
 - a history of hypersensitivity to IFN α
 - 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:^{18,19}
 - 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.²⁰
- Maintenance phase: 10 MU/m² subcutaneously three times per week for 48 weeks.
- Laboratory tests should be performed weekly during the IV induction phase and monthly during the SC maintenance phase.²¹
 - CBC and differential, platelets, LFT's.
 - 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.^{22,23,24} These side-effects may hamper reaching and maintaining the dose needed for maximal therapeutic effect.²⁵
 - 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:²⁶
 - 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 IFN_{α2b} therapy²⁷

Special Considerations

- The successful administration of IFN_{α2b} 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 IFN_α 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 IFN_α 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.²⁸

Follow-Up

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

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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