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Overview

Adjuvant Interferon Therapy for Patients at High Risk for Recurrent Melanoma: An Updated Systematic Review and Practice Guideline

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Abstract

After complete resection of melanoma, some patients remain at high risk for recurrence. The efficacy of adjuvant systemic therapy has been inconsistent in randomised trials and remains controversial. An updated systematic review was conducted to identify new evidence on the role of adjuvant interferon therapy in patients with high-risk resected primary melanoma. Outcomes of interest included overall survival, disease-free survival (DFS), adverse effects and quality of life. MEDLINE, EMBASE, Cochrane Library and the proceedings of the American Society of Clinical Oncology were systematically searched to identify new randomised controlled trials, systematic reviews or meta-analyses. An updated meta-analysis of trials comparing high-dose interferon alpha with observation alone was conducted. The new data are presented in this review. Seven randomised controlled trials met the inclusion criteria: six trials of interferon alone and two trials of interferon plus chemotherapy. Two meta-analyses of adjuvant interferon alpha were also identified. Overall survival was not significantly different between adjuvant high-dose interferon and observation alone (hazard ratio 0.93; 95% confidence interval 0.78–1.12; $P = 0.45$). A meta-analysis of DFS showed a significant benefit for high-dose interferon over control (hazard ratio 0.77; 95% confidence interval 0.65–0.92; $P = 0.004$). One trial reported a significant DFS benefit for pegylated interferon over observation alone. Our updated literature review indicates that adjuvant interferon therapy does not confer a significant long-term overall survival benefit in patients with high-risk resected primary melanoma; however, a significant DFS benefit for high-dose interferon or pegylated interferon treatment has been shown. An revised practice guideline was developed based on the systematic review.

Key words: Adjuvant; chemotherapy; immunotherapy; interferon-alpha; melanoma; systematic review

Statement of Search Strategies Used and Sources of Information

The MEDLINE (July 2005 to June week 2, 2010), EMBASE (week 32, 2005 to week 24, 2010) and Cochrane Library (2010, Issue 2) databases were systematically updated in OVID using a revised literature search strategy. The search strategy for trials of interferon therapy is presented here. In MEDLINE, the term 'melanoma:.mp.' was combined with treatment-related terms, including the Medical Subject Heading terms 'chemotherapy, adjuvant', 'drug therapy', 'immunotherapy' and 'interferons' and the text words 'adjuvant', 'immunotherapy:', 'chemotherap:', 'interferon:' and 'IFN:'. These terms were combined with a search filter designed to identify randomised trials, systematic reviews and meta-analyses adapted from a strategy developed by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk). Modifications were made to the search terms where appropriate for use in EMBASE. The proceedings of the 2006 to 2010 American Society of Clinical Oncology (ASCO) annual meetings were also searched for abstract reports of relevant studies.

Introduction

Melanoma is the most serious form of skin cancer, accounting for only 5% of all skin cancer cases but 80% of skin cancer deaths. The incidence and mortality rates of

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cutaneous malignant melanoma have risen dramatically over the past several decades, faster than those of any other malignancy. The incidence of malignant melanoma in Canada continued to increase in 2009, although mortality was stable in men and decreasing by 0.8% per year in women [1].

Surgical management remains the primary modality of therapy for patients with malignant melanoma; however, despite significant improvements in the early detection of melanoma, some patients remain at high risk of recurrence after definitive surgery. The rate of recurrence ranges from 30 to 90% and usually results in death from melanoma [2].

Although interferon alpha is the best studied agent for the adjuvant therapy of resected melanoma, trial results over the past decade have been inconsistent [3–6]. Clinical studies evaluating high-dose interferon after definitive surgery have generally shown a decrease in cancer recurrence and relapse with no consistent benefit in overall survival or reduction of distant metastases. However, relapse-free survival (RFS) and disease-free survival (DFS) are important end points, as patients are willing to accept toxicity for a modest benefit and improvement in quality of life without a benefit in overall survival [7].

Due to the inconsistencies in trial results, some regard high-dose interferon alpha as standard therapy, whereas others do not. Moreover, interferon has modest toxicity and imposes greater fiscal burdens in the short term on the cancer care system and on patients or their payers. The Melanoma Disease Site Group (DSG) felt that it was important to conduct an updated systematic review of the efficacy of adjuvant interferon therapy in the management of patients who are at high risk for a recurrence of melanoma.

A practice guideline report on systemic adjuvant therapy for patients at high risk for recurrent melanoma was originally completed by the Melanoma DSG in 1998. With the availability of new evidence and the adoption of a newer American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma [2], the report was rewritten in 2005. Practice guideline and systematic review manuscripts based on that report were published in peer-reviewed journals in 2005 and 2006 respectively [8,9] and a subsequent update was made available on the Cancer Care Ontario website (http://www.cancercare.on.ca/). This previous guideline involved a systematic review of adjuvant systemic therapy for high-risk melanoma from 1980 to 2004. At that time there were three randomised trials for high-dose interferon with conflicting results and five randomised controlled trials of low-dose interferon trials that did not show a benefit in overall survival.

Because of the availability of additional new evidence, the Melanoma DSG chose to conduct another update of the evidence and recommendations. This report summarises the evidence published between July 2005 and June 2010 that informed the development of revised recommendations for adjuvant interferon therapy by the Melanoma DSG. The complete practice guideline report is available from the Cancer Care Ontario website (http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34373).

Materials and Methods

This practice guideline was developed by the Melanoma DSG of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle [10]. The practice guideline is 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.

Question

What systemic therapy should clinicians recommend to patients who have been rendered disease free after the resection of cutaneous melanomas and who are at high risk for subsequent recurrence?

Outcomes of interest include overall survival, DFS, adverse effects and quality of life.

Target Population

These recommendations apply to adult patients with high-risk malignant melanoma who are rendered disease free after resection. High risk is defined as patients in the following clinical states:

- primary melanoma with tumour thickness $\geq$4.0 mm;
- primary melanoma with in-transit metastases;
- positive sentinel lymph nodes;
- primary melanoma with regional lymph node metastases that are clinically apparent;
- regional lymph node recurrence; or
- involved nodes were excised but there was no known primary melanoma.

The target population includes those patients who would now be classified as AJCC stage IIB, IIC and III.

Development of Recommendations

Evidence was selected and reviewed by two members of the PEBC Melanoma DSG and a methodologist. This systematic review is a convenient and up-to-date source of the best available evidence on systemic adjuvant therapy for patients at high risk of recurrent melanoma published between July 2005 and June 2010. The body of evidence in this review is primarily comprised of mature randomised controlled trial data. Recommendations were developed by the PEBC Melanoma DSG based on the updated systematic review.