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Health-related quality of life in patients with high-risk melanoma randomised in the Nordic phase 3 trial with adjuvant intermediate-dose interferon alfa-2b ☆

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ABSTRACT

Purpose: To compare health-related quality of life (HRQoL) and side-effects in patients with high-risk melanoma participating in a randomised phase III trial of adjuvant interferon alfa-2b (IFN).

Patients and methods: A total of 855 patients with histologically verified resected cutaneous melanoma in AJCC stage IIb (T4 N0 M0) or stage III (Tx N1-3 M0) were randomised to: Arm A: observation only ($n = 284$); Arm B: 1-year treatment: induction: IFN alfa-2b, 10 MU (flat dose), SC, 5 days/week, 4 weeks, maintenance: IFN alfa-2b, 10 MU (flat dose), SC, 3 days/week for 12 months ($n = 285$); or Arm C: 2 years of same treatment as Arm B. HRQoL was assessed using The European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) before randomisation and at 8 pre-defined time-points during 2 years. IFN-related side-effects were assessed by a study-specific questionnaire.

Results: >80% of eligible patients returned questionnaires at the different assessment points. Statistically significant interactions between randomisation arm and time after randomisation were found for almost all EORTC QLQ-30 variables. While patients in Arm A improved or remained at baseline levels; patients in Arms B and C reported decreased functioning and quality of life, and an increase in side-effects during their treatment. Patients in Arm B improved after the 12th month assessment, when IFN treatment was scheduled to end, to the 16th month assessment ($p < 0.001$). The same pattern of improvement was found for 5 of 7 interferon-related side-effects.

Conclusion: A significant negative impact on HRQoL of IFN treatment was demonstrated, however the impact were reversible when treatment was stopped.

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1. Introduction

Significant improvement of overall and recurrence-free survival (RFS) in high-risk melanoma by adjuvant therapy with high-dose interferon alfa-2b (IFN alfa-2b) was demonstrated in the EST 1684 trial.[1] This was the original impetus to perform 'The Nordic IFN trial' (Clinical Trials gov. #NCT01259934), a randomised trial evaluating whether adjuvant therapy with intermediate-dose IFN had the same beneficial effects on overall and disease-free survival in high-risk melanoma as high-dose IFN.[2] An additional aim was to study if 2 years of treatment was more efficient than 1 year. Between 1996 and 2004 a total of 855, high-risk melanoma patients in Denmark, Finland, Norway and Sweden were included. The conclusion was that adjuvant intermediate-dose IFN in high-risk melanoma patients significantly improved RFS without increasing overall survival. There was no indication that prolonged maintenance of IFN-treatment from 1 to 2 years improved the outcome.[2] Health-related quality of life (HRQoL) was also prospectively investigated.

A number of studies have reported psychiatric morbidity related to IFN treatment.[3–5] Although there are some prospective comparative follow-up studies,[6–8] to our knowledge, only few studies report on HRQoL at several assessment points during IFN treatment.[9,10] These studies showed significant negative HRQoL effects of IFN treatment during treatment. In the present study, both the effects of IFN therapy as well as the effects of its termination on HRQoL were evaluated.

The aim of this paper was to compare HRQoL in the three study arms of the Nordic Adjuvant IFN trial (Arm A = untreated control; Arm B = 1 year of IFN treatment; Arm C = 2 years of IFN treatment) before randomisation and at eight pre-defined time-points during the following 2 years. Of special interest were assessments at 6 and 16 months after randomisation. At the 6 months assessment, patients in Arms B and C were still on IFN treatment treated, but initial side-effects of the drug were anticipated to have decreased. Thus, this point in time represents patients HRQoL during IFN treatment. At the 16 months assessment, Arm B had completed IFN treatment four months earlier, and HRQoL after termination of the IFN therapy was investigated.

2. Patients and methods

2.1. Patients

Patient inclusion criteria of the Nordic Adjuvant IFN trial were: histologically verified resected cutaneous melanoma, AJCC stage IIb (T4 N0 M0) or stage III (Tx N1-3 M0), age $\geqslant$18 years, ECOG performance status 0–1, normal bone marrow function and adequate liver chemistry and renal function. Patient exclusion criteria were: unknown primary or non-cutaneous melanoma, incompletely resected or distant metastatic disease, other malignancies, ongoing treatment with corticosteroids or non-steroidal anti-inflammatory drugs, prior neurologic or psychiatric condition potentially interfering with IFN therapy and prior adjuvant radiotherapy, chemotherapy, or immunotherapy for melanoma.

2.2. Treatment regimens

Arm A consisted of observation only-patients (n = 284). Patients in Arm B received 1 year of treatment: induction: IFN, 10 MU (flat dose), sc, 5 days/week, 4 weeks, maintenance: IFN, 10 MU (flat dose), sc, 3 days/week for 12 months (n = 285). Arm C, the same induction regimen as Arm B, however maintenance therapy included IFN, 10 MU (flat dose), sc, 3 days/week for 24 months (n = 286). Adjuvant intermediate-dose IFN was delivered with moderate and expected toxicities in both treatment arms.[2]

2.3. Randomisation

Randomisation was performed after written informed consent at the Clinical Trial Unit, Department of Oncology, Karolinska University Hospital, Stockholm, Sweden. The patients were stratified according to (1) country and (2) tumour stage at randomisation.

2.4. Points of assessment

HRQoL was assessed before randomisation and 1, 3, 6, 9, 12, 16, 20 and 24 months after randomisation. After informed consent, the baseline questionnaire was handed to the patient to be completed before information about the result of randomisation was given. The questionnaire was returned to the HRQoL study coordinator in a prepaid envelope by the patient. At subsequent points of assessment, questionnaires together with instructions and prepaid envelopes were sent by mail from the study centre in each country. One reminder was sent to those who did not respond within 2 weeks.

2.5. Instruments

The European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) Version 2 was used.[11] Version 2 consists of 30 items and constitutes five functional subscales, one global quality of life subscale, three multi-item symptom scales, and six single items. The validity and reliability of the Swedish version of the EORTC QLQ-C36 have been established.[13,14] Reference values for EORTC QLQ-C30 from the Swedish general population have been published.[15]

2.6. Study-specific questionnaire: 'Side-effects of IFN treatment'

No standardised, validated, or reliability-tested questionnaires assessing the side-effects of IFN treatment were available when this study started. A study-specific questionnaire was developed based on a questionnaire used in the EORTC 18991 trial.[9] Seven items concern symptoms associated with IFN treatment (fever, chills, stiff muscles, headache, numbness in the hands or feet, alopecia and sweating). The same four categories response format (from 'not at all' to 'very much') as in the EORTC QLQ-C30 was used.