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Original Research

Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB–III cutaneous melanoma patients comparing intermediate doses of interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity

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Abstract ***Background:*** We report on the long term outcome of the EORTC 18952 adjuvant interferon (IFN) trial in 1388 resected stage IIB/III melanoma patients and identify key predictive factors for outcome.
Methods: We analysed outcome of the EORTC 18952 trial (4 weeks of IFN, 10 MU, 5 times/week for 4 weeks followed by 12 months IFN at 10 MU, 3 times/week versus followed by 24 months IFN at 5 MU 3 times/week versus observation) regarding relapse-free survival (RFS), distant metastasis-free interval/survival (DMFI/DMFS), and overall survival (OS), and analysed potential predictive factors of outcome.

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Findings: At a median follow-up of 11 years, the comparison of IFN 13 months versus IFN 25 months versus observation yielded estimated hazard ratios (HR) for RFS of 0.94 versus 0.84 (p = 0.06); for DMFI 0.95 versus 0.82 (p = 0.027); for DMFS 0.95 versus 0.84 (p = 0.07); and for OS 0·95 versus 0.84 (p = 0.08), respectively. The impact of treatment was greatest in the ulceration group, whereas in patients with non-ulcerated primaries the impact was null (HR ≥ 1.0). In patients with ulcerated melanoma the HR for IFN 13 months versus 25 months versus observation were for: RFS 0.82 (p = 0.16) versus 0.61 (p = 0.0008); DMFS 0.76 (p = 0.06) versus 0.57 (p = 0.0003); OS 0.80 (p = 0.13) versus 0.59 (p = 0.0007). In stage IIB/III-N1 (microscopic nodal involvement only) patients with ulcerated melanoma the HR estimates were for: RFS 0.85 versus 0.62; DMFS 0.80 versus 0.56; OS 0.77 versus 0.54.
Conclusions: This long term report of the EORTC 18952 trial demonstrates the superiority of the 25-month IFN schedule and defines ulceration of the primary as the overriding predictive factor for IFN-sensitivity.

1. Introduction

An increasing number of patients with regional positive lymph nodes (stage III) are being diagnosed each year, and their prognosis depends on various prognostic factors [1]. Breslow thickness, mitotic index, and ulceration of primary melanoma are the strongest prognostic factors for the presence of micrometastasis in regional lymph nodes [2]. Likelihood of systemic metastatic disease in stage III patients correlates closely with microscopic versus palpable nodal disease and with number of positive nodes [3]. In patients with stage IIIA, IIIB, or IIIC disease, recurrence rates have been reported to be 37%, 68% and 89%, respectively [4]. Within the positive sentinel node (SN) population heterogeneity remains important, correlating with SN tumour load defined by the Rotterdam criteria [5–7].

The efficacy of adjuvant therapies with interferon-alpha-2b (IFN) in melanoma patients is modest at best. Meta-analyses of phase III trials demonstrated that IFN has an effect on relapse-free survival (RFS) but not or only a marginal effect on overall survival (OS) [8–10]. No relationship with dose or duration of treatment with outcome was observed. Apparently only a minority of patients are sensitive to IFN and these patients should be identified. The meta-analysis of the two largest adjuvant trials ever conducted, EORTC 18952 (intermediate doses of IFN) [11] and EORTC 18991 (long term dosing of Pegylated-IFN) [12,13] in 2644 patients demonstrated that both tumour load in the lymph nodes and ulceration of the primary are independent predictive factors for adjuvant IFN therapy [14]. Ulceration of the primary was the overriding important predictive factor for IFN-sensitivity. This has also been shown in the largest meta-analysis reported in 2014 [10]. The enduring impact of ulceration was confirmed by a death rate reduction of 40% in the long term follow-up analysis of the EORTC 18991 trial [13]. Here we present long term follow-up analysis (median 11 years) of the EORTC 18952 trial (ClinicalTrials.gov NCT00002763).

2. Patients and methods

2.1. Patients

Patients 18–70 years of age with cutaneous melanoma stage IIB (T4N0M0)–IIIA/B/C (anyTN1-2M0), with either microscopic involvement (N1) or palpable nodal involvement (N2) of regional lymph nodes, entered the study after adequate surgery of the primary tumour and complete lymph node dissection (stage III). Exclusion criteria included a.o. presence of distant metastasis, prior systemic therapy for melanoma, non-cutaneous melanoma, prior malignancy within past 5 years, autoimmune disease, corticosteroid use, uncontrolled infections and cardiac, renal and hepatic disease.

All patients provided written informed consent before randomisation. The protocol was approved by the EORTC protocol review committee and the local institutional ethical committees.

2.2. Study design

Patients were randomly assigned in a 2:2:1 ratio to one of three groups: 13-month treatment or 25-month treatment with subcutaneous IFNα-2b (Intron A, Schering-Plough, Kenilworth, New-Jersey, United States of America [USA]), or observation. Treatment comprised an induction phase of 4 weeks of 10 million units (MU) of IFNα-2b, intravenously (5 d per week), followed by a maintenance phase, either 10 MU three times a week for 1 year or 5 MU three times a week for 2 years, subcutaneously, i.e. a total dose of 1760 MU in both treatment groups. Stepwise dose adjustments (10 MU to 5 and 3 MU per injection during the induction phase, and from 10 MU to 5 and 3 MU during the maintenance phase in the 13-month treatment arm,