Health-related Quality of Life, Fatigue, and Depression Under Low-Dose IFN-α Therapy in Melanoma Patients

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Summary: Adjuvant melanoma treatment with interferon-α (IFN-α) has proven to be accompanied by several side effects and to decrease patients' health-related quality of life (HRQOL), fatigue and depression being essential factors at that. Although a large body of evidence exists for HRQOL under IFN-α therapy, we now specifically address this topic combining the HRQOL survey in the first months of IFN-α low-dose treatment with a structured assessment of relevant neuropsychiatric side effects, fatigue and depression, with specific validated assessment tools. The present study is a longitudinal observational study assessing fatigue, depression, and HRQOL with specific assessment tools at 3 assessment points over 6 months. The IFN-α treatment group consisted of 48 patients with current IFN-α therapy (3 MU 3 times weekly) from a consecutively recruited melanoma collective and compared with a parallelized nontreatment group (n = 48) in routine clinical practice. A descriptive analysis and generalized linear models were applied to compare the groups. Physical fatigue increased significantly within the first months of IFN-α treatment, whereas cognitive and emotional fatigue and depression symptoms did not show this increase. The hypothesis of a significant deterioration of HRQOL after IFN-α initiation was not confirmed. The treatment group did, however, show a different course of global HRQOL than the comparison group, with a significant improvement in the nontreatment group. Patients under low-dose IFN-α therapy primarily suffer from physical side effects, mainly physical fatigue, in the early phases of treatment. The HRQOL improvement evident in the nontreatment group was not observed in the IFN-α group.

Key Words: melanoma, interferon-α, health-related quality of life, depression, fatigue

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The therapeutic management of malignant melanoma has undergone promising changes over the past years.[1] However, interferon-α (IFN-α) remains the only approved agent in adjuvant melanoma treatment, despite the recent significant developments of targeted therapies in metastatic melanoma.[2–4] Although no international consensus exists on optimal interferon dosage and schedules, the recent German S-3 guidelines recommend 18 months of low-dose IFN-α for high-risk melanomas (stages II–III according to the American Joint Committee on Cancer (AJCC) classification of 2009[5]), with an optional offer of high-dose IFN-α for stage III patients.[2] Identification of the optimal IFN-α treatment regimen is still pending, as existing meta-analyses have failed to identify the optimal dose and duration of treatment.[4,6] Treatment recommendations therefore have to be based on the benefit versus side effects deliberation of the different regimens.[4,7] IFN-α treatment is accompanied by several side effects and a deterioration of patients' quality of life.[8–12] Side effects range from physical flu-like symptoms, which mainly appear in the first weeks of treatment, to longer lasting hepatic and hematopoietic symptoms and psychiatric side effects, including fatigue, depression, and anxiety.[8–11,13,14] Fatigue and depression are 2 of the most common neuropsychiatric side effects of IFN-α therapy and they are a frequent cause for dose reduction or interruption of treatment.[13,15,16] Although fatigue has been found with an incidence of 80%–90%, IFN-α-induced depression rates vary largely between studies depending on the assessment tools and the IFN-α treatment regimen employed.[13,15,17,18] Studies indicate that IFN-α toxicities are most pronounced in the first 4–12 weeks, particularly in the high-dose regimen.[9,19] Large randomized controlled IFN-α trials have previously added the assessment of health-related quality of life (HRQOL) to the evaluation of effectiveness[9,12] but, to our knowledge, only 1 study has investigated the longitudinal course of depression, fatigue, and HRQOL simultaneously. The study showed a significant increase from baseline to the 6-month assessment in somatic complaints, depression, and fatigue with a concurrent reduction in HRQOL in 16 patients treated with high-dose IFN-α.[10] As low-dose therapy is the predominant IFN-α treatment regimen in Germany,[2] detailed knowledge on these side effects in the course of low-dose treatment is crucial for adequate interventions assuring patients' quality of life and treatment adherence. Within large multicentre trials conducted by the Dermatologic Cooperative Oncology Group (DECOG-Trials) the examination of treatment with low-dose IFN-α, has shown inconsistent findings regarding the course of global HRQOL and functioning.[9,20] Therefore, there is a need to address both HRQOL and predominant toxicities under low-dose IFN-α, to determine the prevalence and distinguish the courses of relevant side effects and HRQOL.

The aim of this study is to concurrently investigate the initial effect of low-dose IFN-α on HRQOL, fatigue and depression, assessed with specific, standardized assessment tools, in comparison with a nontreatment comparison group under standard clinical settings. We hypothesized to find an increase in fatigue and depression symptoms in the

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first months of IFN-α treatment associated with a decrease of global HRQOL in comparison with no significant changes in the nontreatment group.

PATIENTS AND METHODS

Sample

The study was part of a broader research project on psychosocial aspects and interventions in melanoma patients and received ethical approval from the Ethics Committees for Medical Research in Freiburg and Cologne, Germany (ClinicalTrials.gov NCT00963261). Between July 2009 and December 2011, a consecutive sample of melanoma patients was recruited in the Skin Cancer Centers of Freiburg and Cologne after giving written informed consent. Patients were asked to participate in this observational questionnaire study if they had histologically proven diagnosis of melanoma, AJCC clinical stages Ib–IIIc.[5] Exclusion criteria were other tumors (except for epithelial nonmetastatic skin cancer) within the past 10 years, permanent infectious diseases, age less than 18 years, or insufficient command of the German language. From July 2009 until December 2011, a total of 466 patients was recruited (Freiburg: N = 288, Cologne: N = 178).

For the present study, a subgroup analysis with patients currently under low-dose IFN-α therapy and a comparable patient group without treatment was conducted. Patients were selected for the analysis based on the following inclusion criteria: (a) tumor stages indicating IFN-α therapy eligibility according to guideline recommendations of 2008 (AJCC clinical stages Ib–IIIc, with ≥ 1.5 mm tumor thickness[21]); (b) completed primary surgery no longer than 2 months before recruitment; and (c) no other adjuvant systemic melanoma treatments. Treatment decisions for the sample were entirely based on the routine clinical practice in the 2 clinics, independent of the study. Patients who started low-dose IFN-α therapy (3 MU 3 times weekly) within 3 months of completing the baseline questionnaire made up the IFN-α treatment group (n = 48). Subsequently, a comparison group parallelized for basic sociodemographic and medical variables without IFN-α therapy was drawn from the remaining sample who also fulfilled the defined inclusion criteria but had declined IFN-α treatment (n = 48). Table 1 summarizes the sample characteristics of the 2 groups, displaying no significant differences between the groups.

TABLE 1. Sample Characteristics by Comparison Group

	Total Sample (n = 96)		
	IFN-α Group (n = 48)	Comparison Group (n = 48)	Comparison of the Groups
Age (y) [mean ± SD]	52.0 ± 14.6	54.2 ± 12.5	$t = -0.81$ $P = 0.42$
Sex (male:female)	30:18	25:23	$\chi^2 = 1.1$ $P = 0.41$
Marriage status			
Married	31	31	
Single	12	9	$\chi^2 = 1.3$ $P = 0.73$
Divorced	2	4	
Widowed	2	3	
Time since diagnosis (mo) [mean ± SD]	1.1 ± 1.2	1.3 ± 0.8	$t = -0.97$ $P = 0.33$
Time since primary surgery (mo) [mean ± SD]	0.1 ± 0.6	0.2 ± 0.4	$t = -1.21$ $P = 0.23$
AJCC clinical stage [n (%)]			
Ib	9 (19)	14 (29)	$\chi^2 = 4.7$ $P = 0.10$
II	22 (46)	26 (54)	
III	17 (35)	8 (17)	

*$P \leq 0.05$.

AJCC indicates American Joint Committee on Cancer; IFN-α, interferon-α.

Procedure

Eligibility of patients was screened before initial contact, and eligible patients were informed of the study and its purpose. Baseline questionnaires (t_0) were distributed in the Skin Cancer Centers and completed within 2 months of primary surgery, with the subsequent questionnaires mailed to the patients in self-addressed stamped envelopes and completed at 3 and 6 months (t_1 and t_2) after baseline. The treatment for the IFN-α therapy group was started between t_0 and t_1.

Measures

Fatigue

Fatigue was assessed with the European Organization for Research and Treatment of Cancer (EORTC) fatigue module, the EORTC QLQ-FA13.[22] This 13-item self-rating scale is the fatigue module of the Quality of Life assessment battery, supplementing the core quality of life questionnaire also used in this study. It consists of 3 subscales (physical, emotional, and cognitive fatigue) and 2 single items indicating "interference with daily life" and "social sequelae" of fatigue. According to the EORTC scoring recommendations, the raw scores are standardized with a linear transformation, so that the standardized scale scores range from 0 to 100.[23]

Depression

Symptoms of depression were assessed with the depression scale of the German version of the Hospital Anxiety and Depression Scale (HADS-D[24]). This scale is particularly appropriate for use with somatically ill patients and has been repeatedly used in melanoma samples to evaluate the level of depression symptoms.[17,25] The outcome score of the depression scale ranges from 0 to 21, with 2 cut-off scores defined by the scoring manual of ≥ 8 for marginal depression and ≥ 11 for moderate depression cases.[26]

HRQOL

The EORTC Quality of Life Questionnaire (EORTC QLQ-C30[27]) was applied as it is a well-validated and commonly used HRQOL assessment tool in IFN-α trials. It consists of 30 items and incorporates 1 global HRQOL score, 5 functioning scales (physical, role, emotional, cognitive, and social), and 8 symptom scales (fatigue, nausea/vomiting and pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea). The global score was selected as the primary HRQOL outcome of this study, with the functioning- and symptom scales comprising secondary HRQOL outcomes.

Statistics

Data were analyzed using SPSS 20 (IBM SPSS Statistics 20; IBM Corporation, Somers, New York). First, the comparability of the 2 groups at baseline was tested using t tests, with independent samples. According to the observational

study design a descriptive analysis of the course of fatigue, depression, and HRQOL of the 2 groups was conducted, by an examination of the mean differences of each group over time. For this purpose the differences in means of t_0 versus t_1 and t_0 versus t_2 were calculated for the treatment and the observation group, respectively. These differences were checked for clinical significance according to the minimally important difference approach, regarding differences of ≥ 10 points on the EORTC scales as clinically significant.[28] To test the significance of differences in fatigue, depression, and global HRQOL across time and compared with the control group General Linear Models (GLM) for repeated measures were conducted. An α-level of 0.05 was used for all statistical tests. The few missing values at baseline (< 5%) were substituted with the group mean values and missing values at t_1 and t_2 were substituted with the last observation carried forward method. A sensitivity analysis without the substitution of missing values was conducted to check for discrepancies. Because the results were comparable we refrained from presenting both analyses.

RESULTS

Comparisons of Baseline Scores Between Groups

The baseline scores on the primary outcome measures of fatigue, depression, and global HRQOL do not differ significantly between the groups ($P = 0.144$–0.597). Thus, the groups were comparable at baseline. Significant differences on the t tests were only found for 2 of the secondary outcome scores: EORTC QLQ-C30 social functioning ($t(94) = -2.06$, $P = 0.04$) and EORTC FA13 social sequelae ($t(94) = 2.22$, $P = 0.03$). These differences suggest lower baseline social functioning and more social hindrances in the IFN-α group and were therefore entered as covariates in the GLM comparing the 2 groups. They did not reveal divergent results (data not shown).

Course of Fatigue, Depression, and HRQOL

Table 2 shows the complete set of mean scores of the scales of the EORTC fatigue module, the HADS depression scale, and the EORTC QLQ-C30 over the 3 assessment points for both the groups. Differences between baseline and the latter scores ($t_1 - t_0$ and $t_2 - t_0$) are presented in the last 2 columns.

Fatigue

The descriptive analysis of differences in the means of the fatigue module showed significant increases in physical fatigue (Fig. 1) and interference with daily under IFN-α. The mean scores of the comparison group did not change considerably on any of the fatigue subscales. The GLM results of the EORTC QLQ-FA13 stress the differential course of physical fatigue of the 2 groups with a highly significant interaction effect ($F_{2,188} = 9.12$, $P = 0.000$). The interaction of time by group was, however, not significant for emotional and cognitive fatigue (Table 3). Although the GLM model for emotional fatigue showed no significant effects, the cognitive fatigue model revealed a significant group effect ($F_{1,94} = 8.19$, $P = 0.005$), indicative of significantly higher cognitive fatigue in the IFN-α group.

Depression

The HADS-D results revealed neither a clinically nor statistical significant change over time in both the groups (Table 2). Thus, no significant increase of depression symptoms under IFN-α was evident in the sample (Fig. 1). The GLM model did reveal a statistically significant group effect ($F_{1,94} = 6.75$, $P = 0.011$), with, however, subthreshold mean HADS-D depression scores in both groups at each assessment point (Table 3). To further analyze this significant group effect, we conducted χ^2 tests to compare the number of patients with elevated depression scores in the 2 groups. This explorative analysis revealed that in both groups no more than 3 patients scored above the cut-off of ≥ 11 without significant differences between the 2 groups at any assessment point (t_0: $\chi^2 = 0.32$, $P = 1.00$; t_1: $\chi^2 = 1.1$, $P = 0.36$; t_2: $\chi^2 = 0.23$, $P = 0.68$).

HRQOL

The main HRQOL outcome (global HRQOL) did not show a clinically significant difference in means over time in the treatment group (Table 2). The GLM model did, however, reveal significant time, group, and interaction effects of global HRQOL (see Table 3 for statistical properties). These significant GLM results are based on a significant improvement of global HRQOL between baseline and the 3 and 6 months' assessment points in the comparison group (+ 9.9 and + 10.8) (Fig. 1). Differences in means between the groups at t_1 (13.6 points) and t_2 (11.7 points) indicate clinically significant lower global HRQOL in the treatment group.

Concerning the secondary HRQOL outcomes the descriptive analysis of the EORTC QLQ-C30 functioning scales revealed no significant changes in the functioning of the treatment group (Table 2). Role and emotional functioning did, however, improve substantially in the observation group over time. Clinically significant increases in the IFN-α group were found on the fatigue, dyspnea, and appetite loss symptom scales.

DISCUSSION

This longitudinal observation study provides a differentiated analysis of HRQOL and relevant side effects after onset of low-dose IFN-α treatment from the patient's perspective in routine clinical practice. We compared the course of fatigue, depression, and global HRQOL of patients at the initiation of IFN-α treatment and the first months of application, with that of a comparable observation group without treatment. Treatment decisions were made in routine clinical practice, independent of the study. Our hypothesis of a significant decrease in global HRQOL at IFN-α onset, as reported in 2 previous low-dose IFN-α trials[9,11] was not confirmed by our data. Loquai et al[29] report similar results for a group of 30 patients under PEG-IFN, with an only marginal HRQOL deterioration, despite several impairments and adverse effects reported by the patients. Garbe et al[20] even found a better global HRQOL and functioning in the low-dose IFN-α group compared with the observation group. A possible explanation for this phenomenon could be that patients receiving IFN-α cope with the treatment side effects in an effective way, resulting in a good HRQOL despite experiencing considerable side effects. Some patients appraise side effects as a sign of effective treatment, which they are willing to tolerate for the benefit of doing what they can to fight the cancer.[30]

However, based on the comparison of the treatment group with the nontreatment group, the present study does implicate a significant effect of IFN-α treatment on HRQOL. Our findings suggest that patients without

TABLE 2. Complete Presentation of Mean EORTC QLQ-FA13, HADS-D, and EORTC QLQ-C30 Scores at t_0, t_1, and t_2 for the IFN-α Group (n = 48) and the Comparison Group (n = 48)

	Baseline t_0	3 mo t_1	6 mo t_2	Difference t_0 Versus t_1*	Difference t_0 Versus t_2*
EORTC QLQ-FA13†					
Physical fatigue					
IFN-α group	30.6 ± 28.6	47.7 ± 29.7	43.2 ± 29.9	17.1‡	12.6‡
Comparison group	23.3 ± 25.1	23.3 ± 28.1	19.1 ± 20.8	0	−4.2
Emotional fatigue					
IFN-α group	20.6 ± 21.9	23.3 ± 23.6	24.2 ± 23.5	2.7	3.6
Comparison group	16.8 ± 21.4	16.0 ± 24.9	15.4 ± 23.6	−0.8	−1.4
Cognitive fatigue					
IFN-α group	13.2 ± 18.4	16.7 ± 20.0	17.6 ± 17.3	3.5	4.4
Comparison group	8.7 ± 13.5	7.4 ± 15.3	6.7 ± 12.5	−1.3	−2.0
Interference with daily life					
IFN-α group	23.6 ± 32.2	43.7 ± 34.5	38.9 ± 30.2	20.1‡	15.3‡
Comparison group	16.3 ± 27.4	16.0 ± 28.3	11.1 ± 19.8	−0.3	−5.2
Social sequelae					
IFN-α group	14.5 ± 27.2	12.5 ± 23.4	17.4 ± 28.3	−2.0	2.9
Comparison group	4.3 ± 16.3	6.2 ± 22.4	3.5 ± 12.4	1.9	−00.8
HADS-D§					
Depression symptoms					
IFN-α group	3.7 ± 3.5	4.0 ± 3.7	4.3 ± 3.5	0.3	0.6
Comparison group	2.9 ± 3.3	2.2 ± 2.7	2.2 ± 2.9	−0.7	−0.7
EORTC QLQ-C30‖					
Global HRQOL					
IFN-α group	64.5 ± 22.7	64.1 ± 22.2	66.9 ± 22.0	−0.4	2.4
Comparison group	67.8 ± 24.3	77.7 ± 23.2	78.6 ± 21.1	9.9	10.8‡
Physical functioning					
IFN-α group	83.5 ± 24.1	79.3 ± 23.1	81.0 ± 19.1	−4.2	−2.5
Comparison group	85.1 ± 15.3	90.3 ± 16.1	91.5 ± 12.5	5.2	6.4
Role functioning					
IFN-α group	61.7 ± 37.5	59.0 ± 32.2	63.2 ± 30.7	−2.7	1.5
Comparison group	66.0 ± 31.9	81.9 ± 30.1	86.1 ± 23.9	15.9‡	20.1‡
Emotional functioning					
IFN-α group	62.1 ± 27.4	63.1 ± 23.7	63.5 ± 24.0	1.1	1.4
Comparison group	66.1 ± 25.5	77.1 ± 26.2	75.5 ± 24.1	11.0‡	9.4
Cognitive functioning					
IFN-α group	76.0 ± 25.5	74.3 ± 27.3	73.6 ± 24.0	−1.7	−2.4
Comparison group	84.0 ± 20.6	87.1 ± 23.9	87.8 ± 19.4	3.1	3.8
Social functioning					
IFN-α group	69.4 ± 29.2	71.9 ± 24.6	72.2 ± 28.6	2.5	2.8
Comparison group	80.9 ± 25.0	87.1 ± 22.3	89.2 ± 19.9	6.2	8.3
Fatigue					
IFN-α group	27.4 ± 26.9	44.7 ± 26.2	40.2 ± 24.4	17.3‡	12.8‡
Comparison group	22.7 ± 24.9	22.9 ± 28.1	18.1 ± 21.1	0.2	−4.6
Nausea/vomiting					
IFN-α group	4.5 ± 13.2	8.7 ± 16.1	7.3 ± 16.8	4.2	2.8
Comparison group	2.8 ± 7.2	2.8 ± 11.0	2.4 ± 10.9	0	−0.4
Pain					
IFN-α group	23.6 ± 30.9	22.6 ± 30.3	26.0 ± 30.9	−1.0	2.4
Comparison group	18.8 ± 25.9	12.8 ± 24.6	13.2 ± 24.1	−6.0	−5.6
Dyspnea					
IFN-α group	11.1 ± 21.0	25.0 ± 31.9	21.5 ± 27.9	13.9‡	10.4‡
Comparison group	15.3 ± 26.6	18.8 ± 26.5	13.9 ± 22.6	3.5	−1.4
Sleep disturbance					
IFN-α group	29.9 ± 39.0	32.6 ± 35.4	38.2 ± 31.5	2.7	8.3
Comparison group	24.3 ± 29.8	17.4 ± 25.7	14.6 ± 23.7	−6.9	−9.7
Appetite loss					
IFN-α group	13.2 ± 24.5	23.6 ± 32.9	18.1 ± 29.1	10.4‡	4.9
Comparison group	6.3 ± 19.0	7.6 ± 20.9	4.9 ± 15.4	1.3	−1.4
Constipation					
IFN-α group	2.1 ± 10.7	5.6 ± 17.3	7.6 ± 20.9	3.5	5.5
Comparison group	2.8 ± 11.6	2.8 ± 11.6	2.8 ± 11.6	0	0

TABLE 2. (*continued*)

	Baseline t_0	3 mo t_1	6 mo t_2	Difference t_0 Versus t_1*	Difference t_0 Versus t_2*
Diarrhea					
IFN-α group	5.7 ± 14.3	12.5 ± 25.4	14.6 ± 24.7	6.8	8.9
Comparison group	4.9 ± 16.8	6.9 ± 18.1	5.6 ± 17.3	2.0	0.7

*Difference calculated as $t_1 - t_0$ and $t_2 - t_0$, respectively.

†Standardized EORTC QLQ-FA13 mean scores, ranging from 0 to 100, ± SD. A higher score represents a higher level of fatigue/interference with daily life/social sequelae.

‡Clinical significance according to Osoba et al[28]: differences of ≥ 10 points on the EORTC scales are regarded as clinically significant.

§HADS-D mean score, ranging from 0 to 21, ± SD. A higher score represents a higher level of depression symptoms. The clinical significance approach of Osoba et al[28] does not apply for the HADS-D score.

‖Standardized EORTC QLQ-C30 mean scores, ranging from 0 to 100, ± SD. On the global score and functioning scales a higher score represents a better HRQOL and functioning. For the symptom scales a higher score represents a higher level of symptoms.

EORTC QLD-C30 indicates European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLD-FA13, European Organization for Research and Treatment of Cancer fatigue module; HADS-D, Hospital Anxiety and Depression Scale; IFN-α, interferon-α.

adjuvant treatment recover better from diagnosis and primary treatment of melanoma, showing a higher HRQOL up to half a year later than patients who undergo IFN-α treatment. Thus, the negative effect of IFN-α on HRQOL is uncovered by the necessary comparison with a nontreatment group. Although social functioning as one aspect of HRQOL had lower baseline values in the IFN-α group, the difference did not affect the outcome on general HRQOL.

The application of specific, validated assessment tools for fatigue and depression in the present study revealed that patients under low-dose IFN-α primarily suffer from physical fatigue, rather than emotional and cognitive fatigue. Physical fatigue increased most substantially within the first 3 months of treatment and stayed elevated through the 6 months assessment point. This multidimensional, detailed investigation adds new insight on the understanding of IFN-α-induced fatigue: patients rather report feelings

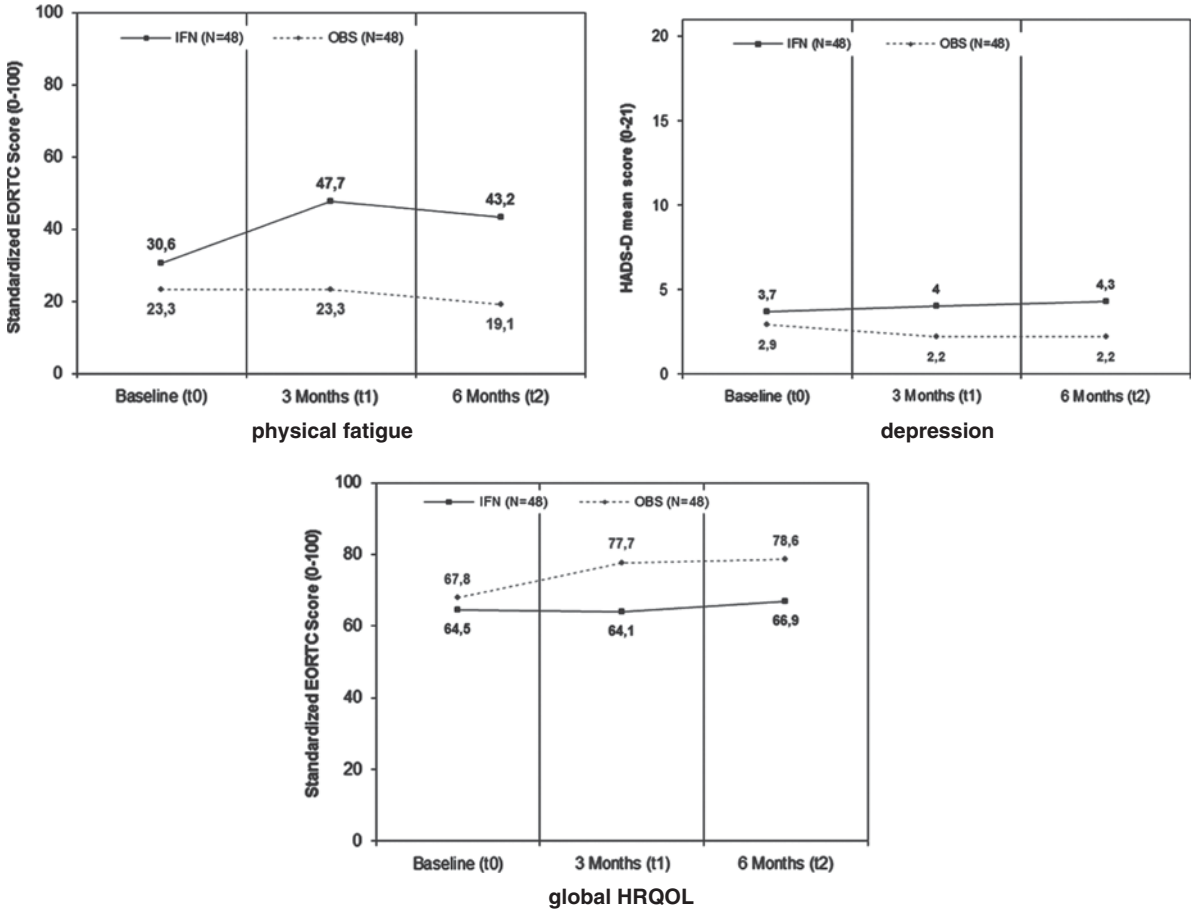

FIGURE 1. Course of physical fatigue depression and global health-related quality of life (HRQOL) of the 2 comparison groups.

TABLE 3. General Linear Model Results for Fatigue, Depression, and Global HRQOL

Scales	Effect	*F* (*df*)	*P*	η^2
EORTC QLQ-FA13 Physical fatigue	Time effect	6.98 (2, 188)	0.001**	0.069
	Group effect	14.59 (1, 94)	0.000**	0.134
	Time × group	9.12 (2, 188)	0.000**	0.088
EORTC QLQ-FA13 Emotional fatigue	Time effect	0.16 (2, 188)	0.849	0.002
	Group effect	2.6 (1, 94)	0.108	0.027
	Time × group	0.77 (2, 188)	0.464	0.008
EORTC QLQ-FA13 Cognitive fatigue	Time effect	0.38 (2, 188)	0.685	0.004
	Group effect	8.19 (1, 94)	0.005**	0.080
	Time × group	2.50 (2, 188)	0.085	0.026
HADS-D Depression Scale	Time effect	0.37 (2, 188)	0.693	0.004
	Group effect	6.75 (1, 94)	0.011*	0.067
	Time × group	2.76 (2, 188)	0.066	0.028
EORTC QLQ-C30 Global HRQOL	Time effect	5.80 (2, 188)	0.004**	0.058
	Group effect	5.34 (1, 94)	0.023*	0.054
	Time × group	3.87 (2, 188)	0.023*	0.040

*$P \leq 0.05$.
**$P \leq 0.01$.
EORTC QLD-C30 indicates European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLD-FA13, European Organization for Research and Treatment of Cancer fatigue module; HADS-D, Hospital Anxiety and Depression Scale; HRQOL, health-related quality of life.

of exhaustion, tiredness and lack of energy in the first months of treatment, than feelings of frustration, helplessness, discouragement, and concentration deficits. This predominantly physical fatigue burden is experienced by many patients as interfering with their daily life. Therefore, IFN-α side effect management should focus on this physical fatigue syndrome, implementing psychosocial interventions specifically aimed at reducing fatigue, which teach patients coping techniques and effective activity management.[31] A recent review on IFN-α-related fatigue offers helpful patient guidelines for the management of fatigue.[13] The authors also point out the strong association of fatigue and depression and the difficulty in their distinction. Our findings suggest that patients suffer considerably more from fatigue than from depression. The potential overlap of physical fatigue and depression in symptoms like lack of energy, exhaustion, and tiredness might be 1 reason for overestimation of depression in other IFN-α trials.[32] In addition, only few IFN-α trials applied specific depression questionnaires.

The generally low mean depression scores of both the treatment and nontreatment group are a striking but unsurprising finding of our study. Heinze et al[15] assessing depressive mood changes under low-dose IFN-α with the Beck Depression Inventory (BDI) also report low mean BDI scores, with only 5% of the IFN-α patients developing clinically significant depressive syndromes under IFN-α. Our data showed mean depression scores in both groups which stayed below normative mean values of the general German population for the whole assessment period,[33] confirming earlier findings of melanoma patients being in general less burdened by psychological distress than other cancer patients.[9,15,17,32] However, patients in the treatment group showed statistically significant higher HADS-D scores than in the nontreatment group, but the number of patients with highly elevated depression levels did not differ between both groups. The study examined the initial effects of IFN-α within the first 6 months of treatment, in accordance to others who have pointed out that most side effects occur in this first treatment phase.[9–10,15] However, depression can also develop as a function of dose and duration[15,18] and should therefore be closely monitored by clinicians throughout the 18 months of treatment to prevent the development of mood disorders.

Summarizing we found IFN-α patients in the Skin Cancer Centers in Freiburg and Cologne to experience an increase in predominantly physical fatigue, concomitant with an interference with daily life and an also clinically significant increase in dyspnea and appetite loss. These findings on physical side effects confirm previous studies and especially appetite loss has shown to be a frequent complain that needs to be addressed with adequate measures in IFN-α side effect management.[9–12,29] In contrast, depression symptoms did not increase significantly in the first months of IFN-α treatment. We believe that our study's differentiated assessment of fatigue, depression, and HRQOL at the onset of low-dose IFN-α in comparison with a nontreatment group is a useful and innovative means of investigating relevant biopsychosocial effects of low-dose IFN-α in routine clinical practice. This observational study design in the routine practice setting entails the chance to close the knowledge gap on HRQOL of patients in routine care units.[29] The nonrandomized study design should, however, also be mentioned as a caveat of the comparison, leading to a limitation of internal validity of our findings and restricting the comparison with findings in cancer trial settings. As treatment decisions regarding IFN-α were not made under study conditions but in clinical practice, possible bias in selecting patients for treatment might have led to underestimation of depression. Dermatooncologists might screen out patients for IFN-α treatment with preexisting burden. Further research on these potential processes in clinical practice along with the examination of long-term effects of low-dose IFN-α are important propositions for further research.

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CONFLICTS OF INTEREST/ FINANCIAL DISCLOSURES

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