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RESEARCH

Psychological Changes in Melanoma Patients During Ipilimumab Treatment Compared to Low-Dose Interferon Alpha Therapy—A Follow-Up Study of First Experiences

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Abstract Immuntherapies are frequently accompanied by psychological side effects. Our goals were to detect the changes of psychological factors (depression, anxiety) among melanoma patients during ipilimumab treatment. Ten ipilimumab treated melanoma patients (Group 1.) and 18 low-dose interferon-alpha treated patients (Group 2.) were compared. In our longitudinal study we measured depression (Zung Self-Rating Depression Scale) and anxiety (State-Trait Anxiety Inventory, STAI). Psychological status was tested four times: in every 3 week during ipilimumab treatment according to the relevant treatment protocol and at baseline, 1st, 3rd and 6th month of interferon therapy. No significant differences were detected at different timepoints in the level of depression or in the anxiety scale in Group 1. However significant increase of depression was found in Group 2 during the 6 months of the study. Increased levels of anxiety were found in the second timepoint in both treatment groups. This increase was only temporary and the level of anxiety returned to the baseline. In our sample no measurable psychological differences were detectable during the 12 weeks treatment period of ipilimumab. Ipilimumab seems to have fewer psychological side-effects compared to other immune therapies.

Keywords Ipilimumab · Interferon · Malignant melanoma · Depression · Anxiety

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Introduction

In the last decades, the incidence of metastatic melanoma has increased [1–4]. With distant metastases (Stage IV) the median survival of patients with melanoma is less than 1 year [5, 6]. The expected 2-year survival rate is 10 to 20 % [7, 8]. For patients with early-stage nonmetastatic disease surgical management remains the mainstay of therapy. Rising incidence rates indicate more effective therapies as adjuvant treatment for patients with malignant melanoma [9].

The development of molecular biology and tumor pathology lead to new treatment options. At present promising drugs are available for the treatment of metastatic melanoma.

Among them ipilimumab is a human monoclonal antibody developed for the treatment of unresectable or metastatic melanoma [10]. Hodi's et al. randomized, controlled trial showed that ipilimumab had a significant improvement in overall survival among patients with metastatic melanoma. The anticytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) antibody ipilimumab was the first immunotherapy that showed a benefit for overall survival in two controlled trials in metastatic melanoma [11]. Its most common adverse events related to the study drugs were immune-related events. Severe autoimmune reactions commonly skin rash, colitis, thyroiditis, hepatitis, hypophysitis may develop in some patients. Depression, confusion, insomnia, mental status changes are named as expected adverse events in ipilimumab treatment [12], but there are only few data in the literature.

Adjuvant interferon immuntherapies were used in several countries. A meta-analysis of 13 randomised trials estimated that interferon alfa reduced the risk of recurrence or death by 13 % and the risk of death by 10 % compared with observation or vaccination, without defining the optimum dose or duration of interferon therapy [13]. Adjuvant interferon, is frequently accompanied by psychological side effects, including anxiety, weight loss, fatigue, irritability, depression, or suicide.

Depression is one of the most common side effects and may lead to discontinuation of therapy [14]. There are several findings about the mechanism of interferon in the central nervous system [15–18]. Inflammatory cytokines may be able to induce neuropsychiatric symptoms such as sickness behavior in animals or depression in humans [19].

The primary aim of this study was to measure psychiatric adverse events, such as changes in depressed mood, and anxiety using psychological self-rating scales during the ipilimumab treatment. Results were compared to the psychiatric side effect profile of low-dose interferon treatment.

Patients and Methods

Two groups were recruited for this study and data were collected in an open-label follow-up design at the Department of Oncodermatology in the National Institute of Oncology (Hungary). All patients signed informed consent to participate in the study, which was approved by the Ethics Committee of the National Institute of Oncology, and the study was carried out in accordance with the Declaration of Helsinki.

Group 1.

Group 1. included ten participants treated with ipilimumab. Patients were eligible for inclusion in the study if they had a diagnosis of stage III or IV melanoma with a life expectancy of at least 4 months and had received previous chemotherapy. Exclusion criteria were pregnancy, breast-feeding, autoimmune diseases and preexisting psychiatric disorders. Description of Group 1. can be seen in Table 1. Patients received 3 mg/kg YERVOY® four times in every 3th week.

Group 2.

The interferon group included 18 participants. Inclusion criteria were tumour thickness of 1.5 mm or thicker, no evidence of regional or distant metastases, except micrometastasis in the sentinel lymph nodes. Exclusion criteria were mucosal or ocular melanoma, pregnancy, breast-feeding, autoimmune diseases and preexisting psychiatric disorders. Patients received interferon-alpha 2a in a weekly dose of 3×3 MIU/week subcutaneuously and they were checked at month 0, 1, 3, 6. Description of Group 2. can be seen in Table 1.

Questionnaires

To detect symptoms of depression, we used the Zung Self-Rating Depression Scale (SDS) [20]. SDS is a self-administered measure of depression severity with 20 items.

Table 1 Description of the study populations

Factors	Group 1. (*N*=10)	Group 2. (*N*=18)
Gender		
Female no.(%)	8 (80)	13 (72.2)
Male no.(%)	2 (20)	5 (27.8)
Age years (range)	60.4 (37; 76)	50.11 (32; 78)
Home		
Capital no.(%)	5 (50)	4 (22)
Town no.(%)	4 (40)	10 (56)
Village no.(%)	1 (10)	4 (22)
Social situation		
Single no.(%)	2 (20)	1 (5.5)
Releationship no.(%)	1 (10)	5 (28)
Married no.(%)	6 (60)	9 (50)
Divorced no.(%)	–	3 (16.5)
Widow no.(%)	1 (10)	–
School		
Primary school no.(%)	2 (20)	2 (11.1)
High school no.(%)	5 (50)	8 (44.4)
University no.(%)	3 (30)	5 (28)
Other no.(%)	–	3 (16.5)
Financial status		
Very bad no.(%)	–	1 (5.5)
Bad no.(%)	3 (30)	6 (33.4)
Average no.(%)	4 (40)	9 (50)
Good no.(%)	2 (20)	2 (11.1)
Very good no.(%)	1 (10)	–
Social support mean (SD)	13.00 (7.902)	10.94 (6.024)

Sum of the item scores was used in the analysis. SDS was validated in the Hungarian population and the cut-off score for clinical depression was 48 [21].

The level of anxiety was measured with State-Trait Anxiety Scale (STAI) in such a way as depression was checked. The

Table 2 Means and standard deviations of depression (SDS) and anxiety (STAI)

		SDS		STAI	
	Time	Mean	SD	Mean	SD
Group 1.	1.week	37.7	4.3	38	10.64
	4.week	38.5	4.95	42.5	9.28
	8.week	39.2	7.48	38.7	11.64
	12.week	38.5	7.5	39.3	12.81
Group 2.	1.week	33.5	5.18	38.17	9
	1.month	35.83	5.1	47.28	10.55
	3.month	37.56	6.1	39.5	8.424
	6.month	41.78	4.28	40.33	7.39

Table 3 Changes in the level of depression (SDS) during the treatment in overall

Depression (SDS)	Variables	F (df)	Sig. (p)
Group 1.	In time overall	3.023 (2.085, 12.507)	0.083
	Week 0. vs week 4.	4.871 (1)	0.069
	Week 0. vs week 8.	0.030 (1)	0.869
	Week 0. vs. week 12.	2.078 (1)	0.200
Group 2.	In time overall	3.176 (2.317; 33.190)	0.047
	Week 0. vs month 1.	0.303 (1)	0.591
	Week 0. vs month 3.	6.253 (1)	0.025
	Week 0. vs month 6.	9.401 (1)	0.008

Results of ANCOVA (F) with the degree of freedom (df) and the level of significance (p). Covariates appearing in the model are: gender, age and social support

STAI presents 20 items describing anxiety states of which the patient records one of four descriptors the degree of distress [22]. Sum of the item scores was used in the analysis. SDS was validated in the Hungarian population and the cut-off score for clinical anxiety was 38.40 (SD=10.66) in men, and 42.64 (SD=10.79) in women [23].

Social support was measured with an adapted social dimension scale developed by Caldwell et al. [24]. Patients had to rate their relationships with important others in the subjectively detected extent. Sum of the item scores was used in the analysis.

Statistics

Data were analyzed be SPSS 21 for Windows. Baseline between group comparisons were evaluated by t-tests (continous variable) and by chi-square test (nominal and ordinal variables; Pearson Chi-Square and Likelihood Ratio) for independent samples. The measured psychometric scores showed normal distribution in our samples (Kolmogorov-Smirnov and Shapiro-Wilk tests). Thus repeated measure of ANCOVA was used to analyse the time-effect of drugs on psychometric measures in the longitudinal data. The repeated measure of ANCOVA was run separately for the 2 study groups because of the differences in treatment schedules. In all ANCOVA Greenhouse-Geiser correction was applied and age, sex, and social support were co-variants. The level of significance was p=0.05, two-tailed.

Results

Baseline

No significant differences were measurable in demographic factors between the two groups. At baseline, Group 1. (ipilimumab) had higher level of depression scores compared to Group 2. (interferon-alpha 2a; t=2.176, df=26, p<0.039). Despite this difference the mean depression score in Group 1. did not reach clinically relevant level as defined by the Hungarian cut-off value (sum score<48).

Regarding anxiety, no significant differences were found at baseline (t=−0.044, df=26, p=0.965) comparing the two study groups and the anxiety level was below the Hungarian cut-off in both groups.

Table 2 shows the means and standard deviations of depression (SDS) and anxiety (STAI).

Drug Effect in Time on Depression

In Group 1. (ipilimumab) there were no significant changes in the depression scores using repeated measure of ANCOVA (Table 3 and Fig. 1). In Group 2. (interferon-alpha 2a) depression scores steadily and significantly increased during the treatment (Table 3 and Fig. 1). Pair-wise comparisons showed significantly higher depression scores at time point 3 and reached its maxima by the 4th time point compared to baseline.

Figure 1 shows the changes in the mean level of depression during the treatment in both groups.

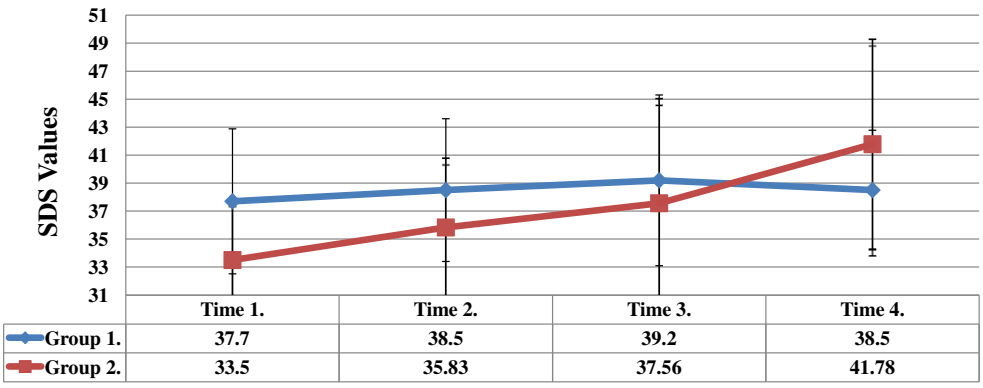

Fig. 1 The change of level of depression during the treatment (mean values of SDS)

Table 4 Changes in the level of anxiety (STAI) during the treatment

Anxiety (STAI)	Variables	F (df)	Sig. (p)
Group 1.	In time overall	1.852 (1.928; 11.570)	0.174
	Week 0. vs week 4.	4.809 (1)	0.071
	Week 0. vs week 8.	5.136 (1)	0.064
	Week 0. vs. week 12.	1.048 (1)	0.346
Group 2.	In time overall	0.261 (2.277; 31.879)	0.853
	Week 0. vs month 1.	0.074 (1)	0.790
	Week 0. vs month 3.	0.330 (1)	0.575
	Week 0. vs month 6.	0.663 (1)	0.429

Results of ANCOVA (F) with the degree of freedom (df) and the level of significance (p). Covariates appearing in the model are: gender, age and social support

Drug Effect in Time on Anxiety

No significant drug effect in time was demonstrated in Group 1. on anxiety scores (Table 4 and Fig. 2). Again, there were no significant changes in the anxiety scores in Group 2. However, in both groups the anxiety scores increased for the 2nd time point but only in Group 2. reached the Hungarian cut-off (Table 4 and Fig. 2).

Discussion

Prevalence of clinically relevant psychological distress among patients with melanoma (all stages) is approximately 30 % [25, 26]. Several of the diagnostic criteria for major depressive disorder are related to symptoms resulting from malignant and chronic disease or its treatment: low energy, poor apetite and impaired concentration. Other psychological symptoms must be also present to have the exact diagnosis of depression: low mood, rumination, grief, hopelessness, demoralization. Meyer et al. [27] gave a thorough summary of cancer associated psychiatric problems. The metaanalysis of Satin et al. showed that depression predicts mortality, but not progression, in cancer patients. Based on data from 25 studies, mortality rates were up to 25 % higher in patients with depressive symptoms [28].

In our study we found significantly (p=0.039) higher baseline level of depression in ipilimumab treated group, compared to Group 2 (interferon). Ipilimumab treated patients had a diagnosis of stage III or IV melanoma with a life expectancy of at least 4 months. Because there were more severe melanoma cases (see exclusion and inclusion criteria) it is not surprising that they suffered from more depressive symptoms at baseline. Other advanced malignancies are often associated with increased level of depression and distress [29].

Not only the stage of disease correlates with psychological side effects. It is well-known that oncological treatments, like adjuvant interferon-alpha, has an impact of psychological factors [30, 31]. Different forms of psychiatric symptoms may be observed in up to 80 % of patients during the treatment. The incidence of clinically relevant depression varies between 20 and 40 % [19]. The increased level of depression and other psychiatric effects deteriorates quality of life which may lead to termination of the therapy. Some of the trials [32, 33] pointed out that interferon loose its effectiveness on recurrence-free survival during treatment discontinuation. Interferon-alpha is an important cytokine in the early immune response. Interferon-alpha may contribute to emergence of mood changes or psychiatric disorders in several ways [19]. Cytokines are, as central effects, mediators for psychiatric disorders by neuropsychoimmunological mechanisms. Interferon-alpha can modulate the activity central neurotransmitters serotonin and glutamate, which are involved in the pathogenesis of several neuropsychiatric disorders [34–36]. Serotonin reuptake inhibitors (SSRI) like paroxetine are able to prevent or reverse depressive symptoms in interferon-alpha-treated patients [37–39]. Our result confirmed the previous findings regarding depression and interferon treatment. We found that depression increased significantly during the interferon treatment (p=0.047), as expected. For the first control point no significant changes were detectable (p=0.591). The increase of depression can be observed from the second timepoint (3rd month) in the interferon treated group. The extent of increase were significant (p=0.025) in this time, and also for the last controll point there were measurable strong significant association (p=0.008) between interferon treatment and the increased level of depression. Our results

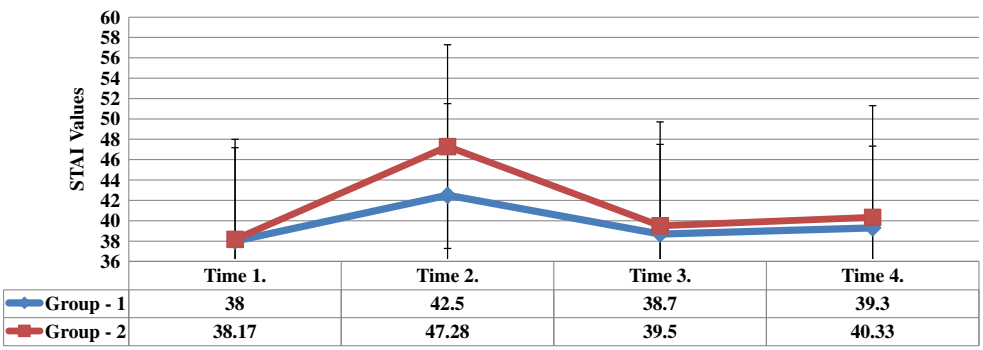

Fig. 2 The change of level of anxiety during the treatment (mean values of STAI)

coincide with the findings of Heinze et al. [40]. They find similar pattern in the increase of depression during low-dose interferon-alpha treatment. They also found that only a low number of participants (5 %) reached the cut-off scores for clinically relevant depressive syndrome during the treatment time. In our study no participant reached the clinically relevant level of depression.

In the ipilimumab treated group there were no significant overall changes in the level of depression during the treatment (p=0.083). No significant differences were measurable comparing the baseline level to the extent of depression at each timepoints. Despite ipilimumab treated patients were in more severe stage of malignant melanoma, interferon treated patients shows greater increase of depression during the treatment time. Probably the different mechanism of drug effectiveness is the reason of different psychological impact. Ipilimumab binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). This T-cell molecule suppresses the immune response. Ipilimumab in melanoma patients has an indirect effect through T-cell mediated anti-tumor immune response. Ipilimumab is a T-cell potentiator that blocks the inhibitory signal of CTLA-4. Suppression of CTLA-4 can augment the immune system's T-cell response in fighting disease. However, in this group there were no further increase in depression during the ipilimumab treatment which suggests that this drug might have less psychological side effects [11, 12].

We found similar level of increase in anxiety at the second timepoint in both treatment groups. This increase was temporarily not significant and baseline level of anxiety returned to the baseline by the time-point 3 and 4 in both groups. These results suggest that increased level of anxiety is not driven by the biological effects of drugs, but rather associated with life events, such as introduction of a new treatment.

Because of the low number of participants, and the open label design no final conclusions can be drawn. Further research including more participants and double-blind design is needed to increase the power of such studies. In addition, longer follow up is required to see the long term effect of the ipilimumab treatment.

In conclusion, in our preliminary study ipilimumab elicited fewer psychological side-effects compared to interferon-alpha immunotherapy which suggests a better side effects profile for ipilimumab treatment that could be especially important in advanced stage melanoma and in patients at risk for depression and anxiety.

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