Psychological side-effects of immunotherapies in the treatment of malignant melanoma

Ph.D. Theses

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1. Introduction

Worldwide the incidence of melanoma is increasing and in spite of advances in local and systemic therapy, mortality continues to rise with 80% of skin cancer-related deaths attributable to melanoma. Similarly, in Hungary the incidence of melanoma has been progressively rising in the past decade. According the data of Hungarian National Cancer Registry and Center of Biostatistics in the last 10 years the number of melanoma cases has doubled in Hungary.

Tumour transplantation models present experimental evidence that tumours can be repressed by the immune system. These findings suggested the existence of tumour-associated antigens and formed the basis of "immune surveillance". Although the idea of cancer immune surveillance resisted widespread acceptance until the 1990s, the better understanding of the mechanisms of immunoediting during tumour progression may provide new insights for improving cancer immunotherapy.

Immunotherapy is a general term referring to artificial activation of the immune system to induce

objective responses and/or disease stabilization. Immunotherapy enhances and encourages the patient's immune system to recognize and destroy cancer cells more effectively. Several types of immunotherapies are used in treating patients with melanoma. Some are being studied as adjuvant treatment. These drugs improve the ability of the body to find and destroy cancer cells. Immunotherapeutic interventions offer the hope for effective treatment against melanoma as it is considered traditionally as an immunogen tumour cancer because of its ability to undergo spontaneous regression.

Interferon

Interferons are pleiotropic molecules that share a number of biologic effects such as antiviral, antiproliferative and immunomodulatory actions. Interferons affect many organs and cause multiple side effects in most of the treated patients. In the long run, adjuvant interferon treatment has the most common and also clinically relevant psychological side effects. Fatigue, anhedonia, social isolation, psychomotor slowness is reported during treatment and is frequently accompanied by psychological side effects including

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depression, irritability, anxiety, or suicide. These psychological problems may lead to a significant deterioration in the quality of life and often result in premature treatment discontinuation. Clinically significant depression developing during interferon therapy varies between 20% and 40% and is one of the most frequent reasons for premature therapy discontinuation. 10%−40% of patients additionally develop a full depressive disorder syndrome that can include suicidal ideation, aboulia, lack of motivation, social withdrawal, guilt, anhedonia, irritability, anxiety, and crying.

Ipilimumab - new therapies

The fast progress in understanding of immunobiology made significant break-through in immunotherapies that have radically changed and renewed the treatment of malignant melanoma. The approval of anti-cytotoxic T-lymphocyte anti-gen 4 (CTLA-4) antibody ipilimumab by US FDA in 2011, as well as the new drugs including antibodies to programmed cell death 1 (PD-1) have extended the potential of immunotherapy for advanced melanoma.

Ipilimumab was the first immunotherapy that showed a benefit for overall survival in two controlled trials in metastatic melanoma.

During ipilimumab therapy, most often autoimmune side effects were reported (colitis, thyreoiditis, hepatitis). Depression, confusion, insomnia, mental status changes are named as expected adverse events in ipilimumab treatment, but there are only few data in the literature.

2. Aims

The chief aim of the research was to measure and identify psychiatric adverse events, such as changes in depressed mood and anxiety using psychological self-rating scales during immunotherapies used in the treatment of malignant melanoma. It was important to identify the factors which could influence the possible psychological (side-)effects of these therapies.

Interferon-induced depression - *first study*

In the first study the primary aim was to investigate the psychological side effects of low-dose interferon treatment in melanoma patients. Specifically, we tested the protective effect of social support on psychological side effects. We hypothesised that

- the level of depression significantly increases during long-term interferon treatment
- the level of anxiety significantly increases during long-term interferon treatment
- different socioeconomic aspects (sex, age, family status, education, financial status) have an effect on emerging depression or anxiety during long-term interferon therapy
- greater social support will be associated with better adjustment (namely less depressive and anxiety symptoms during treatment)

Ipilimumab vs. interferon - *second study*

The primary aim of this study was to measure psychiatric adverse events, such as changes in depressed mood during ipilimumab treatment and compare the results to the psychiatric side effect profile of long-term low-dose interferon treatment. We hypothesised that

- both immuntherapies are associated with long-term psychiatric side effects including depression and anxiety
- the ipilimumab-treated group has increased baseline level of depression and anxiety
- significant increase in the level of depression and anxiety will occur during ipilimumab treatment
- significant increase in the level of depression and anxiety will be observable during long-term interferon treatment

3. Methods

In this thesis two study paradigms were described.

Recruitment and design

Patients were recruited at the Department of Oncodermatology in the National Institute of Oncology (Budapest, Hungary) for the two open-label follow-up studies. All subjects completed a psychological questionnaire booklet.

Background questionnaire

Demographic data, including sex, age, home, family and financial status, and level of education were assessed by a standardised background questionnaire in both study.

3.1. Interferon-induced depression – *first study*

3.1.1. Participants

127 patients were recruited for this open-label follow-up study. All patients received interferon alpha 2a treatment in a weekly dose of 3X3 MIU/week

subcutaneously and regularly attended control examinations at month 0, 1, 3, 6, 9, 12.

3.1.2. Questionnaires

The Beck Depression Inventory was used to detect symptoms of depression.

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms.

Social support was measured with the Social Dimension Scale developed by Caldwell et al.

3.1.3. Other measures

The data of thickness and invasion of primary tumour (Breslow's depth and Clark invasion) were determined by histopathological examinations.

3.1.4. Statistics

Data were analysed by SPSS 21 for Windows (IBM). Repeated measures ANCOVA was used to analyse the effect of interferon treatment during the follow-up on psychometric measures. In all calculations

ANCOVAs Greenhouse-Geisser correction was applied and age, sex, financial status, social support, education were co-variants. The level of significance was p=0.05, two-tailed.

3.2. Ipilimumab vs. interferon – *second study*

3.2.1. Participants

Two groups were recruited for this study:

IPI-Group: included 10 participants treated with ipilimumab. Patients received 3 mg/kg YERVOY® four times in every 3rd week. Patients were controlled at week 0, 3, 6, 9.

The interferon group (**INF-α-Group)** included 18 participants (independent from the previous study). Patients received interferon-alpha 2a treatment in a weekly dose of 3X3 MIU/week subcutaneously and they were checked at month 0, 1, 3, 6.

3.2.2. Questionnaires

To detect symptoms of depression, we used the Zung Self-Rating Depression Scale (SDS).

The level of anxiety was measured with the State-Trait Anxiety Inventory (STAI).

Social support was measured with an adapted version of the Social Dimension Scale developed by Caldwell et al.

3.2.3. Statistics

Data were analysed by SPSS 21 for Windows. Between-group comparisons were evaluated by t-tests and by chi-square tests. Repeated measures ANCOVA was used to analyse the time-effect of drugs on psychometric measures in the longitudinal data. In all calculations ANCOVAs Greenhouse-Geisser correction was applied and age, sex, and social support were co-variants. The level of significance was $p=0.05$, two-tailed.

4. Results

4.1. Interferon-induced depression - *first study*

4.1.1. Baseline results

At baseline none of the patients had depression or anxiety scores above the Hungarian cut-off score for clinical depression or anxiety. Higher educated patients, patients with better financial conditions and male patients scored lower on BDI compared to the other group. There were no significant differences in BDI depression scores at baseline according to social support, family status or tumour parameters.

At baseline women and subjects with very bad or bad financial situations scored higher on the STAI-State anxiety subscale compared to the other groups. There were no significant differences according to the other investigated factors.

4.1.2. Longitudinal effect of interferon treatment on depression

In the study group, BDI depression scores steadily and significantly increased during the treatment. Among the investigated co-variants only social support showed a significant effect on the increase of BDI depression scores. According to post-hoc pair-wise comparisons, social support effect became significant at month 9 and with increasing effect at month 12.

4.1.3. Effect of high versus low social support on depressogenic side effects of interferon treatment

To further investigate how social support modulates the depressogenic side effect of interferon treatment two social support groups were classified according to the mean value of Social Dimension Scale scores: patients in **Group 1** (N=65) had scores above 15, so this was the better-supported group, and in **Group 2** (N=62) subjects scored 15 or below 15, so this group contained the lower-supported patients. The BDI depression score difference steadily increased between the two groups from the visit at month 6. The better-

supported group scored lower from this point compared to the other group and the difference reached significance at month 9 .

4.1.4. Longitudinal effect of interferon treatment on anxiety

There were no significant changes in STAI state anxiety scores during interferon treatment in spite of a temporary increase at the first control visit (month 1).

Sex had a significant main effect on interferon treatment-induced anxiety symptoms. Post hoc analysis demonstrated that female patients had increased anxiety scores from month 6 compared to males. No other co-variants in the model had a significant effect on STAI state anxiety scores during the treatment.

4.2. Ipilimumab vs. interferon – *second study*

4.2.1. Baseline results

No significant differences were measurable in demographic factors between the two groups. At baseline, IPI-Group (ipilimumab) had higher level of depression scores compared to INF-α-Group (interferon-alpha 2a; t=2.176, df=26, p<0.039).

Regarding anxiety, no significant differences were found at baseline (t=-0.044, df=26, p=0.965) comparing the two study groups.

4.2.2. Drug effect in time on depression

In IPI-Group there were no significant changes in depression scores using repeated measures ANCOVA. In INF-α-Group depression scores steadily and significantly increased during treatment.

4.2.3. Drug effect in time on anxiety

No significant drug effect in time was demonstrated in the IPI-Group on anxiety scores. There were no significant changes in anxiety scores in the INF-α-Group. In both groups anxiety scores increased for the 2nd time point.

5. Conclusions

The above studies further supported that immunotherapy of melanoma patients increases the risk of psychological distress. We demonstrated that anxiety and depression are differentially influenced by interferon alpha treatment. Only depression but not anxiety increased significantly during the 12-month follow-up. In addition, the depressogenic side effect of interferon alpha treatment can be diminished by increased social support. Finally, we demonstrated that ipilimumab has fewer psychological side effects than interferon alpha, probably because of the different biological pathways they act through.

The main findings and conclusions of the studies:

- the studies provided evidence for the protective effect of social support in the development of low-dose interferon alpha treatment-induced depression in melanoma patients

- the results suggest that environmental effects such as social support are able to moderate the depressogenic effect of activation in the pro-

inflammatory cytokine pathway, possibly by acting through overlapping biological processes

- significant effect of interferon alpha treatment on anxiety could not be demonstrated

- female patients had significantly more anxiety symptoms from the 6th month of the therapy compared to male patients

- thus depressive symptoms and anxiety symptoms are not equally influenced by the pro-inflammatory cytokine pathway

- no significant drug effect was demonstrated in ipilimumab-treated patients on anxiety scores

- no significant drug effect was demonstrated in ipilimumab-treated patients on depression scores

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

- our studies further support the importance of taking positive and negative environmental

factors into consideration to be able to identify risk biomarkers or genes for depression.

In conclusion, although both IFN-alpha and immune checkpoint inhibitors increase tumour-specific immune response, their psychological side-effect profiles are strikingly different. Thus our results emphasize that considering psychiatric and psychological history beside oncological indications during treatment choice may advance personalised treatment in melanoma patients.

6. List of publications related to the thesis

<u>Kovács P</u>, Pánczél G, Borbola K, Juhász G, Liszkay G. (2014) Psychological changes in melanoma patients during ipilimumab treatment compared to low-dose interferon alpha therapy-a follow-up study of first experiences. Pathol Oncol Res, 20(4):939-944. **DOI: 10.1007/s12253-014-9777-7**

<u>Kovács P,</u> Pánczél G, Balatoni T, Liszkay G, Gonda X, Bagdy Gy, Juhasz G. (2015) Social support decreases depressogenic effect of low-dose interferon alpha treatment in melanoma patients. J Psychosom Res, 78(2015):579-584.**DOI: 10.1016/j.jpsychores.2015.03.005**

<u>Kovács P</u>, Pánczél G, Balatoni T, Pörneczy E, Lőrincz L, Czirbesz K, Gorka E, Melegh K, Liszkay G. (2015) A melanoma immunterápiájának pszichológiai aspektusai. Onkológia, 59(2):93-98.

<u>Kovacs D</u>*, <u>Kovacs P</u>*, Eszlari N, Gonda X, Juhasz G. (2016) Psychological side effects of immune therapies: symptoms and pathomechanism. Curr Opin Pharmacol, 29:97-103. **DOI: 10.1016/j.coph.2016.06.008**
      * *Equally contributed*