Streszczenie w wersji angielskiej

Treatment results analysis of malignant melanoma patients receiving immunotherapy anty-PD-1 with the assessment of prognostic value of clinical parameters, the baseline level of leucocyte subpopulations and immunohistochemical expression of protein products of the mismatch repair genes.

ABSTRACT

Introduction

The improvement of prognosis in advanced melanoma patients is connected with incorporation of immune checkpoints inhibitors PD-1 into clinical practice. However, there is a big differentiation in the immunotherapy responses. The clinical spectrum of treated patients includes subgroups gaining long-lasting remission as well as those with no benefit from the treatment. The discrepancy of the treatment results indicates the need to support individual clinical procedure and defining prognostic and predictive factors for immunological treatment.

Aims of the study

1. The treatment results analysis of advanced malignant melanoma patients from Hollycross Cancer Center, who received immunotherapy anty-PD-1 so as to identify parameters which determined patients' prognosis.
2. The estimation of correlation between baseline blood leukocyte subpopulations and the overall survival and progression free survival as well as the assessment of prognostic value of the above mentioned parameters.
3. The assessment of immunohistochemical expression of mismatch repair genes protein products among malignant melanoma patients, the identification of prognostic value of presence or absence of the estimated proteins.

Material and methods

The material for the study consists of a group of 50 patients with the advanced malignant melanoma from the Holycross Cancer Center receiving immunotherapy antyPD-1 between 1 July 2016 and 30 June 2019. The patients have been the whole group that started immunological treatment using niwolumab and pembrolizumab in the świętokrzyskie province in this period of time.

The statistical analysis of the following parameters was performed among the patients in the study group:

1. Demographic features (age, sex) and clinical parameters: general health status (ECOG), BRAF mutation status, type and line of immunotherapy, stage status according to AJCC classification, baseline LDH level, pattern of visceral tumor involvement, the best radiological response, overall response rate and disease control rate.
2. The assessment of treatment related adverse effects and the percentage of the patients who stopped the treatment because of the immunological toxicity.
3. Baseline level of estimated leucocyte subpopulations (lymphocytes, neutrophils, monocytes, eosinophils, basophils) with neutrophil to lymphocyte ratio in particular. 4. The status of immunohistochemical expression of mismatch repair genes protein products (MLH1, MSH2, MSH6 and PMS2).

Results

We observed a significant difference between the results of the treatment naive patients and the group who received immunotherapy after progression on the first line treatment. 3-year overall survival for the first line treatment was 38% and mOS 18,1 months. In case of the second line treatment, 3-year overall survival was 8% with mOS 9,5 months. The percentage of patients without progression during the 3 years from the beginning of the treatment was 19% for the first line therapy and 0% for the second line. Median PFS reaches 4,9 months and 3,6 months respectively (1 vs 2 line).

The significant prognostic value was related to general health status (ECOG 1), age (<55), stage status (M1c+M1d), the amount and the pattern of visceral tumor involvement. The correlation between the best radiological response and mOS and mPFS was shown. The level of occurrence of grade 1 or 2 adverse effects was connected with the risk of death reduction.

In univariate and corrected analysis there was confirmed a significant correlation of baseline absolute neutrophil count (ANC), relative neutrophil count (RNC) and NLR ratio with the shorter mOS and mPFS. The higher relative lymphocyte count (RLC) showed positive prognostic significance and correlation with longer mOS and mPFS. The highest statistical significance was evaluated for NLR ratio, for which the optimal cut-off negatively correlated with overall survival was ≥4,1. For evaluation of 1-year death risk, the cut-off level was estimated on ≥4,5.

Among the patients with no expression of any MMR proteins, no objective response was observed. The assessment of MMR proteins was not significantly correlated with mOS but mPFS for the patients with no expression of MLH1 and PMS2 protein was considerably lower (3 months vs 9 months, p=0,039).

Conclusions

1. General health status, age <55 years, pattern of visceral tumor involvement and stage status according to AJCC classification have significant influence on overall survival and progression free survival for the advanced melanoma patients. The most important clinical risk factors include worse general health status and the presence of the neoplastic spread to many organs, including the brain metastases.
2. The second line treatment with anty-PD-1 antibodies, especially after previous iBRAF+iMEK inhibitors, is less effective and brings lower response rate or long term survival.
3. The presence of immunological adverse effects does not deteriorate long term treatment results while the occurrence of grade 1 or 2 adverse effects was connected with the risk of death reduction.
4. The prognostic significance for the advanced melanoma patients is connected with the baseline level of lymphocytes and neutrophils, therefore growing NLR level correlates with the significantly shorter overall survival and progression free survival
5. No data were achieved for the prognostic or predictive value of dMMR status for the malignant melanoma patients.