Clinical and Immuno-pathological Biomarkers Associated with Clinical Outcome of Advanced Melanoma Patients Treated with Ipilimumab

Doctoral Thesis

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1. Introduction

Historically, advanced, unresectable melanoma is a disease with poor prognosis; until recently, patients with metastatic melanoma had a median life expectancy of around 8 months, with limited treatment options that did not impact survival.

Immunotherapeutic modalities of cancer treatment have been increasingly gaining ground in the past few years. Understanding the mechanisms regulating antitumor immune response led to the development of a new class of immunotherapeutic agents targeting molecular interactions blocking T cell activation, the so called immune checkpoint inhibitors.

The first such agent, ipilimumab, which blocks CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) was added to the therapeutic arsenal of advanced melanoma in 2011.

It also paved the way for agents targeting other immune regulatory pathways, of which antibodies blocking PD-1 represent the most promising treatment modality in advanced melanoma, especially in combination with the CTLA-4 inhibitor therapy.

In a significant part of responding patients, immune checkpoint agents induce durable remission, showing unprecedented clinical efficacy.

Nevertheless, only a small proportion of patients benefit from the CTLA-4 inhibitor therapy, long-term survival was observed in approximately 20% of patients.

On the other hand, serious side effects, often immune-related, were reported to occur in a higher percentage of patients.

To improve the benefit/risk ratio of individual patients, it is of primary importance to search for biomarkers that could predict the likelihood of therapeutic effect.

Several candidates have been suggested, mainly concerning peripheral blood immune cells or serum factors.

A major drawback of most of the potential markers is that they become evident only during the course of treatment, thereby making them unsuitable for upfront patient selection. Thus far, no reliable predictive parameter is established in daily clinical routine that can be used for the identification of patients who benefit from ipilimumab.

2. Objectives

1. Evaluating the efficacy of ipilimumab in real-life setting, including response rate, best overall response, disease control rate, progression-free and overall survival.

2. Evaluating the toxicity of ipilimumab, analyzing the correlation between immune-related adverse events, toxicity and efficacy.
3. Identifying easily accessible biomarkers associated with clinical response and survival that can be used for the identification of patients who benefit from ipilimumab.
4. Exploring tumor-infiltrating immune cells as potential biomarkers of response to ipilimumab and survival in patients with metastatic melanoma.

3. Methods

3.1. Clinical markers, efficacy and toxicity

This was a retrospective analysis of a consecutive series of all patients administered with ipilimumab 3 mg/kg for melanoma at the National Institute of Oncology (Budapest) between 2010 and 2015. Patients were treated intravenously with ipilimumab 3 mg/kg every 3 weeks, for a maximum of four doses. During the induction phase, clinical examination, adverse event monitoring and laboratory tests were performed before each drug infusion. CT scans of the brain, chest, abdomen and pelvis were carried out at 12, 16 and 24 weeks after the first ipilimumab infusion.

Response was classified according to Immune-related Response Criteria 4.0, adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Candidate biomarkers, comprising LDH, erythrocyte sedimentation rate (ESR), absolute lymphocyte, neutrophil and eosinophil counts (ALC, ANC, AEC) were evaluated in peripheral blood or serum samples collected within 10 days before the first ipilimumab dose. Full blood count analysis was performed with an automatic cell counter, grading of tumor-infiltrating lymphocytes (TILs) has been assessed in a semi-quantitative way on HE-stained slides of the primary melanoma. Mutations were tested using polymerase chain reactions (PCR) covering BRAF exon 15 (codon 600), NRAS exon 2 (codons 12, 13) and NRAS exon 3 (codon 61), preferentially in metastases.

Descriptive statistics were used to present patient's characteristics, safety and efficacy of treatment. Mann-Whitney U-test and Fisher's exact test were used to evaluate the association of baseline variables with clinical response. Progression-free survival (PFS), and overall survival (OS), were estimated with Kaplan-Meier test, median follow-up time was estimated by the reverse Kaplan-Meier method.

Prognostic models for PFS and OS using baseline blood cell counts and serum markers were derived using binary partitioning algorithm. The log-rank test was used for univariate analysis to assess the association of patient characteristics and blood parameters with PFS and OS.

Cox proportional hazard regression model was applied to determine the impact of confirmed single factors. Results were presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Throughout the analysis, p values ≤0.05 were considered statistically significant. All analyses were carried out using the Statistica software version 12.5 (Statsoft, Tulsa, OK).

3.2. Tumor-infiltrating immune cells

Archived paraffin blocks of surgical tissue samples were collected from patients with metastatic melanoma who received ipilimumab treatment from 2010 to 2014 at four centers in Hungary.

In the study, we included only cases with available tumor samples excised within 1 year before ipilimumab therapy and the study population consisted of 30 patients. Eighty-six samples were selected for the investigations: 52 lymph node metastases and 34 subcutaneous/cutaneous metastases.

Response assessment was based on Immune-related Response Criteria 4.0. Patients were considered "responders" if the best overall response was complete or partial response, or stable disease lasting for at least 6 months. Three-micrometer sections from formalin-fixed, paraffin-embedded tumor samples were used in the study.

Immunohistochemistry was performed using monoclonal antibodies against CD4, CD8, CD16, CD20cy, CD45RO, CD68, CD134, CD137, FOXP3, NKp46, and PD-1. For detecting staining, we used 3-amino-9-ethylcarbazole for visualization, and hematoxylin counterstaining.

Counting of labeled cells was performed by light microscope equipped with an eyepiece graticule, independently by two researchers who were blinded to the clinical information. The number of the labeled cells within the metastases was registered in at least 10 randomly chosen fields per section, using the graticule of 10×10 squares designating an area of 0.0625 mm2 at 400× magnification. These fields were blindly chosen from different, non-adjacent areas of the metastases, omitting necrotic areas.

Cutoff levels were set up for each marker, based on the median of the given variable in the whole patient cohort. The proportion of patients with a mean cell density higher than the cutoff level was determined. We used the Mann–Whitney U test for the statistical evaluation of differences in cell densities between different patient groups, χ^2 test for comparing the proportions of samples with high cell densities, and the Pearson test for analyzing correlation between the densities of the

different cell types. The Kaplan–Meier method and Mantel-Cox test were applied for evaluating survival. Univariate and multivariate Cox regression analyses were also performed using mean immune cell densities and patients' age as continuous, while patient gender, disease stage, ECOG status, number of organs involved, LDH level, and previous treatments (chemo- and radiotherapy) as categorical variables. Differences were considered significant in the case of p values ≤0.05. Statistics were calculated using the BMDP Statistical Software Pack.

4. Results

4.1. Clinical markers, efficacy and toxicity

From December 2010 to July 2015, 47 patients received ipilimumab, 34 patients within the expended access program and 13 patients after licensing. Patient and treatment characteristics are presented in Table 1.

Table 1: Patients' characteristics

Patients' and tumors' characteristics	Value	Patients' and tumors' characteristics	Value
Number of patients	47	Age – median (range)	57 (26-83)
Gender, n (%)		Brain metastasis, n (%)	
Male	27 (57)	Present	6 (13)
Female	20 (43)	Absent	41 (87)
Primary tumor T categories, n (%)		Location of primary tumor, n (%)	
T1-T2	15 (32)	Skin	44 (94)
T3-T4	25 (53)	Uveal	2 (4)
Unknown	7 (15)	Mucosal	1 (2)
TIL in primary tumor, n (%)		ECOG, n (%)	
Present	19 (41)	0	35 (75)
Absent	18 (38)	1	12 (25)
No information	10 (21)	2	0
Mutation, n (%)		AJCC stage, n (%)	
BRAF+NRAS-	18 (38)	III irresectable	6 (13)
BRAF-NRAS+	8 (17)	IV M1a	6 (13)
BRAF-NRAS-	13 (28)	IV M1b	10 (21)
Unknown	8 (17)	IV M1c	25 (53)
Previous therapy lines, n (%)		Number of metastatic organs, n (%)	
1	19 (40)	<3	34 (72)
≥2	28 (60)	≥3	13 (28)
Baseline LDH value, n (%)		Ipilimumab cycles, n (%)	
≤1,5x upper normal limit	35 (75)	1	4 (8)
>1,5x upper normal limit	11 (23)	2	2 (4)
No information	1 (2)	3	6 (13)
		4	35 (75)
Following therapies to ipilimumab, n (%)			
BRAF inhibitor	6 (13)		
PD-1 inhibitor	6 (13)		
Ipilimumab reinduction	3 (6)		
Cytostatic	18 (38)		
No therapies	24 (51)		

Of the 47 evaluated patients, 19 (40%) experienced immune-related adverse events, including 6 (13%) grade 3-5 events. The most common irAEs were grade 1-2 dermatologic reactions (n=17, 36%) and gastrointestinal toxicities (n=6, 13%, including two grade 3-5 events).

The best overall response rate (irBORR) was 17% (12% complete response and 5% partial response). Ten patients (24%) experienced stable disease as their best response, whereas the remaining 25 patients (60%) had progressive disease (PD). Disease control rate at week 24 was 40%.

Investigating serum and blood parameters as well as clinicopathologic characteristics for possible associations with treatment response, we found that baseline AEC and ELR were higher in patients with progressive disease when compared with non-PD patients at week 12. The difference remained significant at week 16 but it disappeared at week 24. Median ESR was higher in PD patients when compared with non-PD patients at week 24. None of the blood count parameters or clinical characteristics was significantly associated with irAEs. The median PFS at a median follow-up of 10 months was 2.7 months. Univariate analysis of pretreatment patient characteristics revealed that LDH>1.5×ULN, AEC>0.1 G/L and ESR>1×ULN, but none of the other clinicopathologic parameters examined, were significantly correlated with diminished PFS.

Disease progression rates were found independent of BRAF and NRAS mutation status.

In a multivariate analysis no variable remained significantly associated with disease progression. The median OS observed from the first cycle of ipilimumab was 9.8 months (95% CI: 4.7–14.9), with a 1- and 2-year survival rate of 40% and 28%, respectively. Univariate analysis showed that factors significantly associated with diminished OS were LDH>1.5×ULN, ESR>1×ULN, NLR≥4, AEC>0.1 G/L, ELR>0.1, performance status >0 and multi-organ disease.

In multivariate analysis, LDH level >1.5×ULN was significantly and independently associated with shorter overall survival, and patients with a baseline LDH≤1.5×ULN had a 3.5-fold reduced risk of death when compared with those with elevated LDH level. The one- and two-year survival rates were 54% and 42% for the LDH-low patients compared with 0% in the LDH-high group.

4.2. Tumor-infiltrating immune cells

In lymph node metastases, mean densities of CD4+, CD8+, FOXP3+, CD134+ lymphocytes, CD20+ B cells, and NKp46+ NK cells were significantly higher in the responder group compared to non-responders.

For each cell type, a cutoff value was introduced based on the median of the given variable in the whole patient group, and the proportion of patients with a mean intratumoral cell density exceeding this value was calculated and analyzed according to the efficacy of ipilimumab treatment.

In this comparison, the above mentioned lymphocyte markers as well as CD137 also showed higher prevalence in the responders than in non-responders.

On the other hand, in subcutaneous/cutaneous metastases significant difference between responders and non-responders was found only in the proportion of patients with high mean density of CD68+ macrophages and CD16+ cells.

When all samples were evaluated together, significant association with response to treatment was found in the case of NK cell density values (p=0.0182) and for proportion of patients with high density of NK cells as well as that of FOXP3+ cells and CD68+ macrophages (Table 2).

Table 2: Relationship of treatment response with proportion of patients with significant mean density of immune cells infiltrating metastases[a]

	Lymph node metastases (No. of patients: 19)			Cutaneous/subcutaneous metastases (No. of patients: 19)			All metastases (No. of patients: 30)		
Immune cell markers	Resp. n=7	Non-resp. n=12	p-value	Resp. n=9	Non-resp. n=10	p-value	Resp. n=13	Non-resp. n=17	p-value
CD4	**6 (86)**	**4 (33)**	**0.0274**	5 (56)	5 (50)	0.8087	8 (62)	9 (53)	0.6377
CD8	**6 (86)**	**3 (25)**	**0.0106**	4 (44)	5 (50)	0.8087	8 (62)	5 (29)	0.0785
CD45RO	6 (86)	6 (50)	0.1195	6 (67)	4 (40)	0.2451	7 (54)	5 (29)	0.1758
CD20	**6 (86)**	**4 (33)**	**0.0274**	3 (33)	5 (50)	0.4625	6 (46)	4 (24)	0.1927
CD134	**5 (71)**	**3 (25)**	**0.0480**	5 (56)	4 (40)	0.4977	8 (62)	5 (29)	0.0785
CD137	**5 (71)**	**2 (17)**	**0.0170**	4 (44)	5 (50)	0.8087	7 (54)	7 (41)	0.4906
FOXP3	**6 (86)**	**1 (8)**	**0.0009**	5 (56)	5 (50)	0.8087	**7 (54)**	**3 (18)**	**0.0371**
PD-1	5 (71)	5 (42)	0.2101	3 (33)	6 (60)	0.1775	6 (46)	8 (47)	0.9607
CD16	5 (71)	6 (50)	0.3615	**7 (78)**	**3 (30)**	**0.0373**	8 (62)	6 (35)	0.1533
CD68	4 (57)	5 (42)	0.5146	**8 (89)**	**3 (30)**	**0.0094**	**11 (85)**	**8 (47)**	**0.0344**
NKp46[b]	**6 (86)**	**4 (33)**	**0.0274**	4 (50)	3 (30)	0.1353	**10 (83)**	**7 (41)**	**0.0232**

[a]Data are presented as number of patients (%). [b]One case with lymph node metastasis could not be evaluated. Significant differences are shown in bold. Resp.: responder, Non-resp.: non-responder

The densities of most of the studied immune cell types strongly correlated with each other and they frequently showed coordinate presence. In lymph node metastases, high expression of at least 7 of the 11 markers studied was found in 6 of the 7 responders (86%), compared to only 3 of 12 non-responders (25%, p=0.0106).

Kaplan–Meier analysis of survival according to the mean immune cell density in lymph node metastases revealed that high densities were associated with significantly longer overall survival in the case of 7 of the 11 cell types studied.

The potential prognostic effect of immune cell densities evaluated as continuous variables (together with disease stage, patients' age and gender, ECOG status, number of organs involved, LDH level, and previous treatments) was also analyzed using Cox's proportional hazards model.

In univariate analysis, CD4+, CD8+, CD45RO+, FOXP3+, and CD16+ cell densities were found significantly associated with overall survival (p=0.0290, p=0.0093, p=0.0180, p=0.0083, and p=0.0047, respectively), besides ECOG status (p=0.0009) and LDH (p=0.0227).

Multivariate analysis including all immune cell density values as well as clinicopathologic parameters identified ECOG status (p=0.001) and FOXP3+ cell density (p=0.004) as significant independent predictors of survival.

Similar associations were found when all samples were evaluated together, using either Kaplan–Meier analysis or Cox regression demonstrating significantly longer survival in case of high number of cells expressing CD4, CD8, CD45RO, FOXP3, CD16, CD68, or CD20 (p=0.0348, p=0.0136, p=0.0113, p=0.0121, p=0.0055, p=0.0168, or p=0.0372, respectively), as well as in cases with better ECOG status (p=0.0026) and normal LDH level (p=0.0006).

In multivariate analysis, LDH (p=0.001) and the amount of FOXP3+ cells (p=0.016) proved as independent predictive factors.

In the s.c./cutaneous location, on the other hand, the mean density of CD16+ and CD68+ cells showed correlation with OS both in Kaplan–Meier analysis and Cox's proportional hazards model (p=0.0197 and p=0.0175, respectively); in this group, only LDH level proved as independent predictor of survival (p=0.002).

5. Conclusions

1. Indicators of clinical efficacy, like response rate, best overall response, disease control rate, progression-free and overall survival were comparable to those observed in previous trials with ipilimumab.
2. Immune-related adverse events were generally manageable, and consistent with the results of earlier studies involving ipilimumab at the same dose. No correlation of toxicity with either efficacy or the evaluated biomarkers was found.

3. In univariate analysis, worse ECOG performance status, high number of organs involved, elevated ESR, elevated baseline serum AEC and ELR had a negative influence on survival. Serum LDH level was the only biomarker that was significantly associated with OS both in univariate and multivariate analysis.
4. Our data suggest that infiltration by FOXP3+ cells, CD4+, CD8+, CD134+ T lymphocytes, CD20+ B cells, and NKp46+ NK cells in lymph node metastases, as well as the prevalence of CD16+ cells and CD68+ macrophages in cutaneous/subcutaneous ones could be considered as candidate predictive markers in melanoma patients receiving ipilimumab therapy.

6. List of Own Publications (ΣIF: 13.869)

Publications included in the dissertation

[1] Balatoni T, Ladányi A, Fröhlich G, Czirbesz K, Kovács P, Pánczél G, Bence E, Plótár V, Liszkay G: Biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. Pathol Oncol Res. 2018 Sep 17. doi: 10.1007/s12253-018-0466-9. IF: 1.935

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