Immune-related adverse events in melanoma patients treated with immune checkpoint inhibitors

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Introduction

Imune checkpoint inhibitors in the treatment of melanoma have brought significant improvements in patient survival, but a new side effect profile has emerged, that is challenging for clinicians. Our aim was to collect and characterize adverse events in patients receiving CTLA4- and/or PD1-inhibitory immunotherapy for advanced melanoma and to compare our results with international literature data.

Patients and Methods

A retrospective analysis was performed at the Department of Dermatology and Allergology, University of Szeged among stage III and IV melanoma patients receiving immunotherapy between 01.01.2017 and 10.10.2019.

Results

Patient demography:

- 88 patients, 42 male, 46 female, mean age: 60.125 y (35-82 y)

Primary melanoma characteristics:

Cutaneous: n=71

- localisation: trunk: 49.3%, extremity: 38%, head and neck: 12.6%
- subtype: NM: 55.2%, SSM: 34.3%, AM: 8.9%, amelanotic: 1,5%
- mean Breslow-thickness: 5.049 mm (0.3-39 mm)
- ulceration: 57.35%
- pT1: 8.57%, pT2: 17.14%, pT3: 31.42%, pT4: 41.42%

Mucosal: n=1 (nasal, pT4)

Ocular: n=4 (choroideal: 1, uveal: 3, pT2: 2, pT4: 2)

Melanoma of unknown primary origin: n=12

TNM, Stage:

- Stage III: 14 (16%) (III.B: 2, III.C/D: 12)
- Stage IV: 74 (84%), (M1c: 27, M1d: 22, M1b: 16, M1a: 9)

(NM: nodular melanoma, SSM: superficial, AM: acral)

Immune-related advers events:

- N of pts with irAE: 32/88 (36%), total N of irAEs: 38
- N of pts with irAEs: CTLA4i+/-PD1i: 75% (3/4), PD1i: 34.5% (29/84)

Frequency of irAEs:

- 42% endocrinological
- 13% dermatological, 13% gastrointestinal/hepatobiliary
- 11% respiratory, 11% musculoskeletal

Grade of irAEs:

- grade 1, 2: 76.3%, grade 3: 23.7%, (grade 4: 0, deaths: 0)

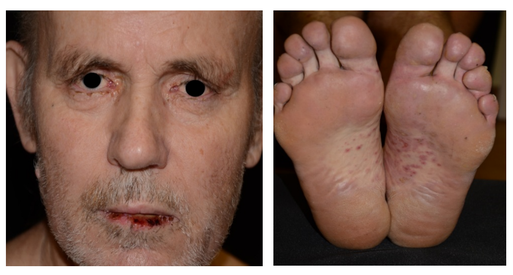
Treatment of pts with irAE:

- systemic steroid: 40% (13/32)
- hormonal therapy: 44% (14/32)

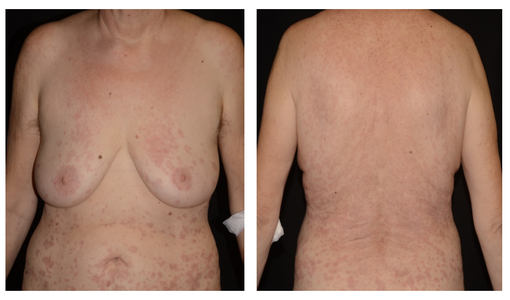
Influence of irAE on immunotherapy:

- continued without interruption: 50% of pts with irAEs
- temporarily suspended: 25%
- permanently discontinued: 25%

Indication, MM stage	Number of pts per treatment	Number of pts and irAEs	Number and type of irAE
Adjuvant (st. III)	PD1i: 8	1 patient 1 irAEs	1 colitis
Metastatic (st. III)	PD1i: 6	2 pts 2 irAE	1 hypothyreosis 1 hyperthyreosis
Adjuvant (st. IV)	PD1i: 6	1 patient 1 irAE	1 myopathy
Metastatic (st. IV)	CTLA4i: 4	3 pts 3 irAEs	1 colitis 1 pneumonitis 1 hyperthyreosis
	PD1i: 64	25 pts 31 irAEs	5 hyperthyreosis 6 hypothyreosis 1 hypophysitis 1 autoimmune diabetes mellitus 3 pneumonitis 1 myositis 2 leukoderma 1 Stevens Johnson synd. 2 dermatitis/rash 1 rheumatoid arthitis exacerbation 1 polyarthritis 1 hepatitis 1 pancreatitis 1 enterocolitis 1 neutropenia 1 Autoimmune hemolytic anaemia exacerbation 1 renal insufficiency 1 urinary infection
88 patients	PD1i: 84 pts CTLA4i: 4 pts	32 patients	38 irAEs



Skin and mucosal lesions in Stevens Johnson syndrome in a 62 years-old male patient after 12 infusions of PD1i. Systemic steroid lead to rapid resolution of symptoms. Immunotherapy was temporarily suspended.



Maculo-papular rash in a 66 y-old female patient. After 2 infusions of PD1i, her preexisting rheumatoid arthritis was exacerbated, after 3 infusions rash, pneumonitis and hepatitis developed. The immuntherapy was permanently discontinued.

Most frequent irAes - comparison with literature data[1-8]

Treatment / Grade	CTLA4i		PD1i	
	Literature data	Own experience	Literature data	Own experience
Grade 1 and 2	1. Skin 2. Gastrointestinal 3. Respiratory 4. Arthalgia	Pneumonitis (n=1) Hyperthyreo-sis (n=1)	1. Skin 2. Gastrointestinal 3. Arthalgia 4. Endocrin	1. Endocrin (n=15) 2. Skin (n=5) 3. Arthalgia (n=2) 4. Hepatitis, colitis (n=2)
Grade 3	1. Gastrointestinal 2. Endocrin 3. Respiratory 4. Skin	Colitis (n=1)	1. Gastrointestinal 2. Endocrin 3. Hepatobiliary 4. Skin	1. Pneumonitis (n=2) 2. Myositis/myopathy (n=2) 3. Pancreatitis, colitis (n=2) 4. Hypophysitis (n=1)

Patients with preexisting diseases		IrAE
Number of pts with preexisting endocrinological disease (n=9)	Hypothyreosis (n=7)	hypothyreosis worsening (n=2) autoimmun diabetes mellitus (n=1)
	Hyperthyreosis (n=1)	hyperthyreosis worsening (n=1)
	Adrenal insuffitiency (n=1)	hypophysitis (n=1)
Autoimmune, immunmediated (n=3)	Psoriasis vulgaris (n=1)	hyperthyreosis (n=1)
	Rheumatoid arthritis (n=1)	RA exacerbation, pneumonitis, hepatitis, rash (n=1)
	Spondylarthrosis (n=1)	-
Endocrinological + autoimmune + immunmediated (n=1)	Hypothyreosis + AIHA + Boeck-sarcoidosis	Autoimmune hemolytic anaemia (AIHA) worsening-crisis (n=1)

Conclusion

Our study confirmed the literature data on the frequency, severity and type of irAEs. We found, that underlying endocrinological and autoimmune diseases are no contraindications for immunotherapy, but there is an increased risk in these patients to develop irAEs. We concluded, that managing irAEs is a major challenge for the onco-dermatology team. To ensure early recognition, it is important that patients, primary and emergency care staff receive detailed information about the potential irAEs. Successful treatment of irAes requires close interdisciplinary collaboration.

References

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