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Characterization of the inflammatory tumor microenvironment composition in brain metastases after failure of immune checkpoint inhibitor therapy

Angelika M. Starzer (1,2), Markus Kleinberger (1), Katharina Feldmann (1,2), Judith Kreminger (1,2), Stefan Traint (1,2), Ariane Steindl (1), Georg Widhalm (3), Brigitte Gatterbauer (3), Karin Dieckmann (4), Matthias Preusser (1,2), Anna S. Berghoff (1,2)

1 Department of Medicine I, Division of Oncology, Medical University of Vienna, Austria, 2 Christian Doppler Laboratory for Personalized Immunotherapy, Department of Medicine I, Medical University of Vienna, Austria, 3 Department of Neurosurgery, Medical University of Vienna, Austria, 4 Department of Radiotherapy, Medical University of Vienna, Austria

Background

Immunotherapy (IO) is an important pillar in the treatment of various advanced solid cancers, but resistance is frequent. We aimed to characterize the inflammatory tumor microenvironment of patients with brain metastasis (BM) progression after IO to gain insight on potential inflammatory resistance mechanisms.

Methods

Patients with BM resection after failure of IO were identified (IO cohort). Tumor-infiltrating lymphocytes (TILs; CD3, CD8, FOXP3) as well as immune checkpoint molecules (PD-L1) were investigated on immunohistochemical stainings. A control group of BM patients without prior IO was included for comparison (no immunotherapy cohort, NIO).

Results

Twenty-eight IO patients (12 females, 16 males; median age 61 years) and 76 NIO patients (41 females; 35 males; median age 58 years) were included in the analyses.

Table 1 – Patient characteristics of IO cohort

IO cohort		N=28	100%
Sex	female	12	42.9
	male	16	57.1
Age at BM diagnosis, years	median (range)	61 (27-78)	
Cancer entity	Lung	14	50.0
	Melanoma	5	17.9
	Breast	1	3.6
	Renal	4	14.3
	Other	4	14.3
KPS at BM diagnosis	median (range)	80 (50-90)	
OS from BM, months	median (range)	7 (0-51)	

Table 2 – Patient characteristics of NIO cohort

NIO cohort		N=76	100%
Sex	female	41	53.9
	male	35	46.1
Age at BM diagnosis, years	median (range)	58 (37-80)	
Cancer entity	Lung	45	59.2
	Melanoma	5	6.6
	Breast	11	14.5
	Renal	4	5.3
	Other	11	14.5
KPS at BM diagnosis	median (range)	90 (40-100)	
OS from BM, months	median (range)	11.5 (0-128)	

Abbreviations: IO immunotherapy, NIO no immunotherapy, BM brain metastases, KPS Karnofsky Performance Status, OS overall survival

Table 3 – IO characteristics of IO cohort

IO characteristics		N=28	%
Systemic therapy lines prior to IO	median (range)	1 (0-4)	
IO last therapy before BM diagnosis	yes	22	78.6
	no	6	21.4
Number of IO applications	median (range)	7 (1-56)	
	n/a	1	3.6
Target of IO	CTLA4 only	2	7.1
	CTLA4+PD-1	4	14.3
	PD-1	14	50
	PD-L1	8	28.6
IO+chemotherapy combination	yes	3	10.7
	no	25	89.3

Abbreviations: IO immunotherapy, BM brain metastases, CTLA4 cytotoxic T-lymphocyte-associated protein 4, PD-1 programmed cell death protein 1, PD-L1 programmed cell death 1 ligand 1

Sixteen/28 (57.1%) IO patients showed tumor PD-L1 expression (TPS range 0-100) in BM. FOXP3+ TIL density was statistically significantly higher in IO compared to NIO patients (Mann-Whitney U test; p=0.001, 77.50 cells/mm2 vs. 27.68 cells/mm2). Median CD8+ TIL density was numerically higher in IO compared to NIO (p=0.066) whereas median CD3+ TIL density was lower in IO vs. NIO (p=0.075) patients, respectively.

Table 4 – Inflammatory characteristics in IO cohort

IO cohort inflammatory characteristics	median	range
CD3+ TIL density	227.17	0.34-2093.71
CD8+ TIL density	325.05	10.45-6372.33
FOXP3+ TIL density	77.50	5.61-1049.46
Tumor PD-L1 expression (>1%)	**N=28**	**%**
positive	16	57.1
negative	12	42.9

Table 5 – Inflammatory characteristics in NIO cohort

NIO cohort inflammatory characteristics	median	range
CD3+ TIL density	467.30	17.92-3087.15
CD8+ TIL density	135.72	5.06-1917.34
FOXP3+ TIL density	27.68	0-323.36

Abbreviations: IO immunotherapy, NIO no immunotherapy, CD cluster of differentiation, TIL tumor-infiltrating lymphocytes, FOXP3 forkhead box P3, PD-L1 programmed cell death 1 ligand 1

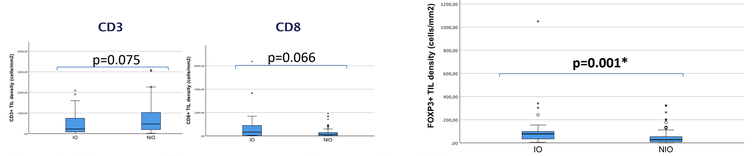

Figure 1 – Differences in TIL densities (cells/mm2) between IO and NIO

Median CD8+TIL density was statistically significantly highest in BM from melanoma patients (Kruskal Wallis test, p=0.001). There was no correlation of time from last IO application to BM resection with TIL density (Spearman correlation coefficient <±0.3).

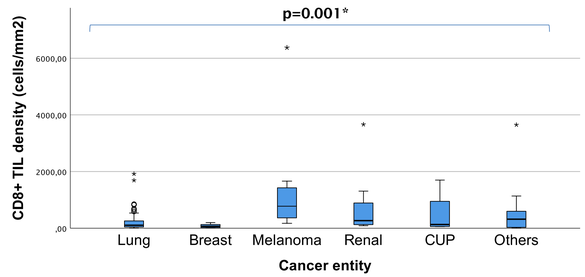

Figure 2 – Differences of CD8+ TIL density according to cancer entity (IO and NIO cohort)

*statistically significant

No significant difference in other subgroups of TILs

Conclusion

A higher infiltration with regulatory immunosuppressive FOXP3+ T cells could be an immunological escape mechanism in BM from solid cancers. New immunological targets are warranted to increase the likelihood of response to IO in BM patients.

References, Disclosure Statement & Contact

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Please contact anna.berghoff@meduniwien.ac.at for any questions