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Brain Metastases as the Most Responsive Metastatic Site to Immunotherapy in Patients with Metastatic NSCLC

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Abstract

Although immune checkpoint inhibitors have revolutionized treatment landscape for patients with non-small cell lung cancers (NSCLC) - influences on brain metastases (BM) are still uncertain due to the fact that these patients have generally been excluded from clinical trials or have been underrepresented. Aim of our research was to investigate if there is a link between the site of metastases with response to immunotherapy.

Study included a total of 141 patients with pathologically confirmed advanced NSCLC with PD-L1 expression ≥50% and treated with immune checkpoint inhibitors (ICI) monotherapy (Pembrolizumab) in front line. Patients were divided into two subgroups according to the presence of CNS metastases, based on which subgroup comparison was performed. All patients with BM, who were enrolled in our study, received stereotactic radiotherapy (SRS) or whole brain radiotherapy (WBRT) in addition to ICI.

ICI significantly prolonged PFS in group with CNS metastases with median of PFS: 11.5 months versus 9 months in the group without CNS metastases (HR= 0.416, p 0.028). There was no statistically significant improvement in OS in the group of patients with CNS metastases compared to a group of patients without baseline CNS metastases (median OS 11,5 months versus 14 months; HR= 0.531, p 0.116).

Our study found that brain metastases in patients with stage IV NSCLC and PD-L1 expression ≥ 50% responded best to immunotherapy. An absopal effect provides a sound potential rationale for our results. In this context, it is crucial to highlight the effects of the synergistic action of immuno- and radiotherapy.

Keywords: NSCLC; Brain metastases; Immunotherapy; Pembrolizumab; Abscopal effect.

Introduction

Brain metastasis is a common complication in lung cancers and represent a negative prognostic factor. Therapeutic options for patients with BM are largely palliative and include surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or their combinations, while chemotherapy is rarely used due to its limitation to effectively cross the blood-brain barrier [1]. These treatments often leave patients with adverse neurocognitive function, poor quality of life, and dismal prognosis [2].

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Although immune checkpoint inhibitors have revolutionized treatment landscape for patients with non-small cell lung cancers (NSCLC) - influences on brain metastases (BM) are still uncertain due to the fact that these patients have generally been excluded from clinical trials or have been underrepresented.

Having in mind that immunologic microenvironment of metastatic disease can vary by specific organ, there is possible impact on the response to immunotherapy, and prognosis as well.

Our research aims to investigate a possibility of a link between metastases site and immunotherapy response.

Patients and methods

The study included a total of 141 patients with pathologicaly/cytologically confirmed advanced NSCLC treated with ICI monotherapy in first line between June 2017. to June 2021. Study was conducted at Clinic for pulmonology, University Clinical center of Serbia. Eligible patients were ≥18 years and Eastern Cooperative Oncology Group (ECOG) performance status was ≤1. Patients treated with Pembrolizumab monotherapy were required to have a programmed death ligand 1 (PD-L1)-positive tumor with TPS ≥50% and they received pembrolizumab 200 mg every 3 weeks. Abscence of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) mutations was mandatory.

Tumor lesions were measured using computed tomography at baseline and every 9 weeks thereafter. Tumor size was recorded as the sum of the longest diameters (SLD) assessed per RECIST v1.1 by independent central review. PD-L1 expression was assessed in contemporaneous biopsy samples using immunohistochemistry.

Patients were divided into two subgroups according to the presence of CNS metastases, based on which subgroup comparison was performed. All patients with BM, who were enrolled in our study, received stereotactic radiotherapy (SRS) or whole brain radiotherapy (WBRT) in addition to ICI.

Descriptive statistics were reported as frequencies and percentages for categorical variables, and medians, standard deviations from the mean (SD), and ranges for continuous variables. Hazard ratios were estimated using the Cox proportional-hazards model. Kaplan-Meier curves were used to estimate mean progression-free survival (PFS) and mean overall survival (OS). Confidence interval of 95% was used for medians and they were calculated using bootstrapping. For testing hypotheses, p-value of <0.05 was considered as significant. Statistical analyses were done using the IBM SPSS ver. 26 software (IBM Corporation, USA).

Results

Overall 141 metastatic NSCLC patients treated with ICI were enrolled in this study. Among them, 84 (59.6%) were men and 57 (40.4%) were women. Median age was 63 [standard deviation (SD) 8,720, range 35-89] years. There were 72 (51.1%) current smokers, 54 (38.3%) former smokers, and 15 (10.6%) never-smokers. The dominant tumor histology was non-squamous [66.0%]. The most frequent metastatic site was lung, detected in 43 patients (30.5%) and followed up by CNS (19.9%). Pleura, bone and liver metastases were detected in 14.2%, 12.8% and 9.9% of patients, respectively.

The baseline clinical and demographic characteristics are reported in Table 1.

The median PFS for all patients was 10 months, median OS was 14 months. Patients were divided into two subgroups: one group included patients with CNS metastases and other included patients without CNS metastases, but with other metastases. ICI significantly prolonged PFS in group with CNS metastases with median of PFS: 11.5 months [95% CI: 8-15 months] versus 9 months [95% CI: 7-13 months] in the group without CNS metastases (HR= 0.416, 95% CI: 0.19-0.91, p 0.028) as shown in Figure 1. There was no statistically significant improvement in OS in the group of patients with CNS metastases (median OS: 11,5 months [95% CI: 8-15 months] versus 14 months [95% CI: 11-15.97 months] compared to a group of patients without baseline CNS metastases; HR= 0.531, 95% CI: 0.24-1.17, p 0.116 (Figure 2).

Table 1: Baseline characteristics and demographics.

Characteristics	CNS metastases	Other metastatic sites
Age (range)	63.5 (43-81)	63 (35-89)
Sex		
Female (%)	14 (50)	43 (38.1)
Male (%)	14 (50)	70 (61.9)
Histology		
Non-squamous (%)	20 (71.4)	73 (64.8)
Squamous (%)	1 (3.6)	26 (23)
NSCLC NOS (%)	7 (25)	14 (12.4)
PDL1 expression		
PDL1 ≤ 60%	10 (15.4)	55 (84.6)
PDL1 61%-80%	7 (16.7)	35 (83.3)
PDL1 > 80%	11 (32.4)	23 (87.6)
Smoking status		
Current smokers	18 (12.8)	54 (38.3)
Former smokers	9 (6.4)	45 (31.9)
Never smokers	1 (0.7)	14 (9.9)
Pack-years (range)	40 (0-160)	40 (0-100)

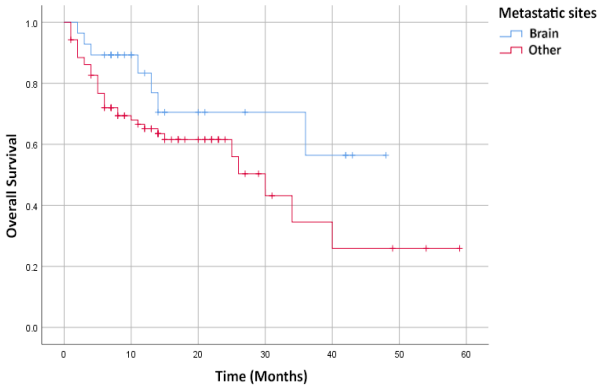

Figure 1: Kaplan-Meier analysis of progression-free survival in patients with brain metastases (blue line) and in patients without brain metastases, but with other metastatic sites (red line).

Discussion

Some retrospective cohort studies suggest that liver, bone, and brain metastases in patients receiving immunotherapy lead to a significant association with worse PFS and OS compared with other sites [3,4].

It is well known that the immunologic microenvironment of metastatic disease can vary by specific organ, with a possible impact on the response to immunotherapy, as well as prognosis [3,5]. For instance, lymphocyte population of the liver is selectively enriched with natural killer (NK) and T cells, which is critical for first-line immune defense against invading pathogens, modulation of liver injury and recruitment of circulating lymphocytes [6]. In the brain, the blood–brain barrier and brain-resident cell types (e.g., microglia) cause an immunosuppressive microenvironment [7].

Brain metastases (BM) occur in 20% to 32% of patients diagnosed with non–small cell lung cancer and generally represent a negative prognostic factor for patients with solid malignancies [8-10]. However, among non-oncogene NSCLC patients with BM there are limited data available on intracranial efficacy of immunotherapy because these patients have generally been excluded from clinical trials or are underrepresented [11].

In the majority of cases BM are approached with locoregional treatments, due to the fact that blood–brain barrier limits the efficacy of some systemic drugs [12]. The mechanism of action of ICIs is based on altered immune cell activity rather than direct action of these agents in the brain [13]. The presence of tumor infiltrating lymphocytes (TILs) and the expression of PD-L1 have been observed in brain metastases from patients with NSCLC and it has been shown that PD-L1 expression is lower in BM compared with the primary tumor [14]. In addition, the administration of ICI in patients with BM may be associated with pseudoprogression and subsequent symptom aggravation due to increased edema before the tumor actually shrinks [11]. This phenomenon may necessitate symptomatic treatment with corticosteroids which could affect the treatment potency.

As shown previously in our study, ICI significantly prolonged PFS in the group with brain metastases compared to a group of patients with other metastases, while there was no statistically significant improvement in the same group OS.

Considering all the above how could we explain that ICI significantly prolonged PFS in group of patients with brain metastases compared with those with other metastases?

All patients with BM, who were included in our study, received stereotactic radiotherapy (SRS) or whole brain radiotherapy (WBRT) in addition to ICI. Therefore, an abscopal effect provides a sound potential rationale for our results.

Many study results suggest that localized radiotherapy , traditionally used to control localized disease, not only directly kills tumor cells but also may elicit an immune response by promoting the cross-priming of tumor-specific CD8 T cells, that attack both irradiated and distant, nonirradiated tumors [15-17]. The RT-induced antitumor T cell response can be enhanced by combination with ICI [18]. The combination of radiation and immunotherapy may increase the occurrence of abscopal effect, [19-21] with rates ranging from 25% to 52% with immune checkpoint inhibitors [19,21].

The results of a retrospective study by Min Wu et al. are consistent with ours. The study included patients with advanced NSCLC who had received radiotherapy for a primary or metastatic solid tumor. They aimed to determine the differences in systemic immune activation after RT to the brain, bone, lung, liver, adrenal gland, and soft tissue during immunotherapy synchronously. Study concluded that irradiation to brain had the strongest effect on immune activation and response to immunotherapy treatment in advanced NSCLC. They assumed that this may be due to the fact that the blood–brain barrier was breached with RT [22]. A meta-analysis conducted by Wenjing Li et al also suggested that PD-1 or PD-L1 inhibitors can reduce the risk of both disease progression and death of patients with brain metastases of NSCLC, who have been pretreated with local therapies and/or in whom the brain lessions are asymptomatic [23].

Conclusion

Our study found that brain metastases in patients with stage IV NSCLC with PD-L1 expression ≥50% responded best to immunotherapy.

Given the fact that all patients received radiotherapy in addition to ICI, it is crucial to highlight the effects of the synergistic action of these two therapies. Further clinical trials are needed to define the role of immunotherapy in NSCLC patients with BM.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

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References

1. Di Giacomo, A., Valente, M., Cerase, A. et al. Immunotherapy of brain metastases: breaking a “dogma”. J Exp Clin Cancer Res. 2019; 38: 419.

2. Pathak R, Amini A, Hill A, Massarelli E, Salgia R. Immunotherapy in Non-Small Cell Lung Cancer Patients with Brain Metastases: Clinical Challenges and Future Directions. Cancers (Basel). 2021; 13: 3407.

3. Botticelli A, Cirillo A, Scagnoli S. et al. The Agnostic Role of Site of Metastasis in Predicting Outcomes in Cancer Patients Treated with Immunotherapy. Vaccines. 2020; 8: 203.

4. Bilen MA, Shabto JM, Martini DJ, Liu Y, et al. Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. BMC Cancer. 2019; 19.

5. Obenauf AC, Massagué J. Surviving at a Distance: Organ-Specific Metastasis. Trends in Cancer. 2015; 1: 76–91.

6. Robinson MW, Harmon C, O'Farrelly C. Liver immunology and its role in inflammation and homeostasis. Cell Mol Immunol. 2016; 13: 267-76.

7. Quail DF, Joyce JA. The Microenvironmental Landscape of Brain Tumors. Cancer Cell. 2017; 31: 326-341.

8. Barnholtz-Sloan, Jill S., et al. «Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System.» Journal of clinical oncology. 2004; 22: 2865-2872.

9. Molinier O, Audigier-Valette C, Cadranel J, Monnet I, Hureaux J, et al. OA 17.05 IFCT1502 CLINIVO: Real-Life Experience with Nivolumab in 600 Patients (Pts) with Advanced Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2017; 12: S1793.

10. Sperduto PW, Kased N, Roberge D, Xu Z, et al. Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases. Journal of Clinical Oncology. 2012; 30: 419-425.

11. El Rassy E, Botticella A, Kattan J, Le Péchoux C, Besse B, et al. Non-small cell lung cancer brain metastases and the immune system: From brain metastases development to treatment. Cancer Treatment Reviews. 2018; 68: 69-79.

12. Eguren-Santamaria I, Sanmamed MF, Goldberg SB, et al. PD-1/PD-L1 blockers in NSCLC brain metastases: challenging paradigms and clinical practice. Clinical Cancer Research, clincanres. 2020.

13. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer. 2012; 12: 252-264.

14. Mansfield AS, Aubry MC. et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. Annals of Oncology. 2016; 27: 1953-1958.

15. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Current Problems in Cancer. 2016; 40: 25-37.

16. Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: Radiosensitisation and potential mechanisms of synergy. Lancet Oncol. 2015; 16: e498-e509.

17. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004; 58: 862-870.

18. Park SS, Dong H, Liu X, et al. PD-1 restrains radiotherapy-induced abscopal effect. Cancer Immunol Res. 2015; 3: 610-619.

19. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology. 2014; 3: e28780-1-e28780-9.

20. Chandra RA, Wilhite TJ, Balboni TA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. Oncoimmunology. 2015; 4: e1046028-1-e1046028-7.

21. Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2—tumor and immunological responses. Sci Transl Med. 2012; 4: 137ra74-1–137ra74-1-7

22. Wu M, Liu J, et al. Systemic Immune Activation and Responses of Irradiation to Different Metastatic Sites Combined With Immunotherapy in Advanced Non-Small Cell Lung Cancer. Front Immunol. 2021; 12: 803247.

23. Li W, Jiang J, Huang L, Long F. Efficacy of PD-1/L1 inhibitors in brain metastases of non-small-cell lung cancer: pooled analysis from seven randomized controlled trials. Future Oncol. 2022; 18: 403-412.