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

Ratkovic A*; Nikolic N; Golubovic A; Pandurevic S; Kontic M

1Clinic for Pulmonology, Clinical Center of Serbia, Serbia.
2Unit of Endocrinology and Diabetes Prevention and Care, IRCCS Azienda Ospedaliero- University of Bologna, Italy.
3School of Medicine, University in Belgrade, Serbia.

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].
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 pathologically/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. Absence 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).

![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).](image-url)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CNS metastases</th>
<th>Other metastatic sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>63.5 (43-81)</td>
<td>63 (35-89)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>14 (50)</td>
<td>43 (38.1)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>14 (50)</td>
<td>70 (61.9)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
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</tr>
<tr>
<td>Non-squamous (%)</td>
<td>20 (71.4)</td>
<td>73 (64.8)</td>
</tr>
<tr>
<td>Squamous (%)</td>
<td>1 (3.6)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>NSCLC NOS (%)</td>
<td>7 (25)</td>
<td>14 (12.4)</td>
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<tr>
<td>PD1L expression</td>
<td></td>
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<tr>
<td>PD1L ≤ 60%</td>
<td>10 (15.4)</td>
<td>55 (84.6)</td>
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<tr>
<td>PD1L 61%-80%</td>
<td>7 (16.7)</td>
<td>35 (83.3)</td>
</tr>
<tr>
<td>PD1L &gt; 80%</td>
<td>11 (32.4)</td>
<td>23 (87.6)</td>
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<tr>
<td>Smoking status</td>
<td></td>
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<tr>
<td>Current smokers</td>
<td>18 (12.8)</td>
<td>54 (38.3)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>9 (6.4)</td>
<td>45 (31.9)</td>
</tr>
<tr>
<td>Never smokers</td>
<td>1 (0.7)</td>
<td>14 (9.9)</td>
</tr>
<tr>
<td>Pack-years (range)</td>
<td>40 (0-160)</td>
<td>40 (0-100)</td>
</tr>
</tbody>
</table>
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 immuno-therapy 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 lesions 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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Ethical statement: The authors received ethical approval for the study from the ethical board and all patients signed ICF.

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References


