

The role of immunotherapy in patients with lung cancer and brain metastases: a narrative review of the literature

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Abstract

Worldwide, approximately half of the patients diagnosed with lung cancer (LC) will develop, simultaneously or asynchronously, brain metastases (BMs). The existence of BMs negatively affects the quality of life and constitutes a poor prognostic factor, linked with high mortality. Locoregional therapy with surgery or radiation is, until now, the treatment of choice, especially for symptomatic patients; however, both options are linked to a high complication rate. The question arising here is whether, in asymptomatic patients, the benefit outweighs the risk and whether an alternative method can be used to treat this special category of patients. Over the last decade, immune checkpoint inhibitors (ICIs) have represented a major breakthrough in the field of oncology, and several molecules have been approved as a treatment option for LC. This review tried to analyze the tumor microenvironment of both the primary lung tumor and the BMs in order to evaluate the intracranial activity of ICIs, outline the main challenges of including these agents in the treatment of LC with BMs, highlight the available information from the main clinical trials, and mark the potential positive effect of choosing a combination therapy. In conclusion, it appears that immunotherapy has a positive effect, inhibiting the progression of BMs, but more data should be published specifically for this category of patients.

Introduction

Lung cancer (LC) is the leading cause of cancer-related mortality worldwide. Over the past 15 years, there have been tremendous advances in LC evaluation, diagnosis, and management. The introduction of screening programs for high-risk individuals with low-dose computed tomography helped in the diagnosis of more early-stage LC. The focus of scientific study in understanding the different pathways of cell proliferation and differentiation has provided a variety of new therapies, increasing the ability to deliver personalized medical care to patients whose, until recently, treatment choices were limited [1].

However, most cases are in an advanced stage at the time of diagnosis, often with distant metastases. Apart from cases of lymphogenous spread, which are particularly common in LC, the most frequent sites of hematogenous metastasis are the liver, the adrenal glands, and the bones, followed by the brain [1]. At the time of the initial diagnosis, approximately 20% of patients with small-cell LC (SCLC) and 10% of patients with non-small-cell LC (NSCLC) have detectable brain metastases (BMs), and an additional 40% will develop them sometime during the course of their disease [2]. BMs can dramatically affect the quality of life, and their pres-

ence is linked with a negative impact on neurocognitive function and a poor prognosis. If untreated, BMs can lead to death, with a median overall survival (OS) of only 1-2 months. Age, extra cranial tumor activity, the number of BMs, and the initial tumor type/molecular subtype are important factors determining patients' prognosis [3]. Given that the incidence of BMs in SCLC can be as high as 80% during the course of the disease, prophylactic cranial irradiation (PCI) is recommended in limited-stage disease. It seems that PCI reduces the risk of BM's appearance and improves the patient's quality of life. It can be applied after the patient's response to first-line systemic therapy [4]. The management of BMs is a clinical challenge and requires a multidisciplinary approach, as there are several potential treatments, each with its own limitations and side effects. Characteristics such as the location and number of BMs, the presence of symptoms, actionable mutations or other extra-central nervous system (CNS) metastases, the performance status, and the patients' preferences are important for the selection of adequate local treatment [5].

Neurosurgical resection is often the standard method of care for solitary or symptomatic BMs since resection rapidly reduces symptoms [6]. However, this is a high-risk procedure that places strict limits on the number and location of the lesions in the brain that are suitable for resection. Whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), for the treatment of limited brain lesions, are also proven to be treatment options [6]. Despite the improved local control rate, there are still serious concerns about the use of these treatment options. Particularly, the importance of WBRT is decreasing due to the related neurotoxicity and deterioration in patients' quality of life, a point that is also highlighted by a phase III trial (QUARTZ) that revealed limited clinical benefit compared with best supportive care [7]. SRS has better neurocognitive and/or quality of life outcomes but is linked to the highest rate of intracranial relapse, and its use might delay the initiation of systemic treatment, which is crucial for such a group of advanced-stage patients [5].

On the other hand, the structure of the brain, with the blood-brain barrier (BBB), makes the role of systemic treatment controversial [8]. Historically, BBB reduces the access and activity of hydrophilic and other large agents into the CNS. Nevertheless, the presence of BMs sometimes alters this structure, resulting in increased exposure to systemic drugs.

Unfortunately, this group of patients is usually excluded from clinical trials, especially with systemic agents; hence, the real-world evidence on efficacy is limited.

Over the last decade, the approach to LC treatment has changed with the introduction of immunotherapy. The tumor microenvironment (TME) is characterized by an overexpression of inhibitory ligands and receptors, which downregulate the immune system, evading the immune response. The two most common clinically targeted pathways include the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways. The CTLA-4 and PD-1/programmed death-ligand 1 (PD-L1) pathways are key immune checkpoint receptors that downregulate T-cells and mediate immunosuppression. CTLA-4 inhibits CD28 costimulation, which is required for T-cell activation. PD-1 is upregulated on active T-cells and binds to PD-L1 or PD-L2, resulting in T-cell suppression [1].

The application of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic approach of LC, significantly enhancing survival outcomes across all stages of the disease, both in NSCLC and SCLC. In the early stages of LC, ICIs serve a crucial role as either a neoadjuvant or an adjuvant therapy. In the

advanced stages, they are utilized in the first- and second-line settings, as single agents or in combination with chemotherapy, irrespective of the histological subtypes [9].

The question of whether ICIs are effective in BMs is challenging, as the available data are limited due to the underrepresentation of these patients in clinical trials. Moreover, even the selected subgroups consist of patients with small, asymptomatic, or previously treated BMs rather than a broader population; therefore, the available results are controversial.

The aim of this review is to summarize the state-of-the-art of clinical evidence for ICIs intracranial activity by exploring the details of the TME of the primary and metastatic sites, outline the main challenges of including these agents in the treatment of LC with BMs, highlight the available information by citing the data of the main clinical trials, and mark the possible positive effect of choosing a combination therapy.

Methods

For this review, articles from databases such as Google Scholar, Clinicaltrials.gov., and PubMed were retrieved, using the keywords "lung neoplasms", "non-small-cell lung cancer", "small-cell lung cancer", "immunotherapy", "immune checkpoint inhibitors", "brain metastases", "brain tumors", "PDL1", "CTLA-4". Only English articles were included, as well as clinical trials, systematic reviews and meta-analyses and some abstracts from international conferences. The references cited in the papers identified were also reviewed.

Differences in the tumor microenvironment between primary lung tumors and brain metastases

In order to assess the potential impact of immunotherapy in treating BMs, it is important to describe and compare the TME of both the primary tumor of the lung and the BMs. Each TME has unique characteristics that distinguish the primary from the metastatic site and determine the response of ICIs [10]. The brain is considered an immune-privileged organ due to the presence of the BBB and the existence of specialized cells such as microglia, astrocytes, and neurons [8]. In contrast to targeted medications that act directly on tumor cells, the mechanism of ICIs is believed to involve the modification of immune cell activity rather than the direct impact on tumor cells in the brain [11].

Furthermore, it has been widely observed that in brain tumors, the balance between the tumor and the microenvironment of the brain is impaired. This frequently results in a breach in the BBB and an infiltration of immune cells from the peripheral circulation [12]. Due to its complexity, many scientific attempts have been made to investigate this microenvironment.

Microglia, as innate immune cells in the brain, play an important role in antigen presentation and immune responses. Upon activation, they release proinflammatory molecules and modulate their surface markers, facilitating the entry of immune cells into the brain through the BBB, thereby promoting angiogenesis and metastasis [13]. BMs primarily contain macrophages derived from peripheral monocytes rather than resident microglia, which are related to different phenotypes and ways of action [14]. Despite the overall reduction in immune cell abundance within brain metastatic tissue, there is an elevation in the proportion of tumor-associated

macrophages (TAMs). This increase directly contributes to tumor growth by releasing specific molecules that impede T-cell proliferation and antigen presentation. TAMs play an immunosuppressive role in the immune context of BMs, and their targeting may be a promising strategy for the approach of BMs [12].

Astrocytes are another brain-exclusive cell type. It appears that brain injury affects astrocytes by producing reactive astrocyte proliferation. Their role is intricate and multifaceted. Firstly, they produce factors like plasmin that fight against the extension of BMs; however, with further interaction, they trigger the release of growth factors, encouraging tumor growth [12,15].

Ikarashi *et al.* used multiplex fluorescence immunohistochemical analysis to evaluate the immune characteristics of the primary lung tumors and the corresponding BMs in 34 patients with NSCLC [16]. The study revealed that BMs have fewer tumor-infiltrating lymphocytes (TILs), such as CD4+ T-cells, CD8+ T-cells, and CD4+Foxp3+, but despite their lower number, they were positively correlated with OS.

Reduced T-cell abundance and infiltration, combined with suppression of antigen presentation (suppressed dendritic cell maturation), lymphocyte extravasation, and leukocyte adhesion (reduced vascular cell adhesion protein 1), contribute to an immunosuppressive microenvironment in BMs [12,14].

In the same context, Chen *et al.* performed a comprehensive TME analysis using an RNA sequencing platform on 86 samples from lung tumors and matched the BMs of 43 individuals with NSCLC [17]. They concluded that in BMs, the enrichment of total immune cells is significantly lower, which is in line with the previous study.

Moreover, the fraction of neutrophils in BMs was higher compared to the primary lung tumor, while, normally, the brain has a lower density. This finding may be linked to the immunosuppressive effects of the brain TME. Since neutrophils were thought to be specialized cells with a low level of transcriptional flexibility, their role in oncogenesis and progression was underappreciated until recently [18]. Without stimulation, neutrophils undergo apoptosis, and the release of harmful enzymes is prevented. The TME, by reprogramming the normal neutrophils, can create tumor-associated neutrophils (TANs), which contribute to cancer growth and spread by attracting macrophages and Tregs, suppressing cytotoxic T-cells and natural killer cells, and increasing angiogenesis [19]. Targeting immunosuppressive TANs may contribute to the management of BMs in NSCLC.

Furthermore, the study mentioned that some immune-related signatures [17], such as the scores of interferon- γ (IFN- γ) and T-cell-inflamed GEP signatures, both predictors of the clinical response to ICIs, were lower in BM tissue. IFN- γ may control various adhesion molecules (such as VCAM-1 and ICAM-1) and chemokines (such as CXCL10), mediating T-cell migration and resulting in BBB disruption [11,20].

Finally, PD-L1 expression in BMs was found to be unrelated to matched primary LC, findings that are similar to previous reports [21].

Kim *et al.* also tried to compare the differences in the immunological TME of the two tumor sites and agreed that in the BM specimen, the density of PD-1+ TILs was markedly decreased, and the infiltration was positively correlated with PD-L1 expression of tumor cells [10]. This might be linked to the contradictory efficacy of ICIs in LC patients with BM.

The presence of TILs is required for the efficacy of immunotherapy. Other immune cells that are part of the brain TME and the metastatic site, such as TAMs, microglia, and astrocytes, are

also involved in tumor progression and immune evasion [11]. The TME of the BMs has a lower number of lymphocytes compared to the primary tumor site; however, a significant lymphocytic response exists, presumably prompting tumor cells to produce the PD-L1 factor [22]. So, there might be an intracranial response to ICIs despite the inadequate amount of TILs. CD8+ T-cells within BMs exhibit reduced activity compared to those in peripheral and normal intracranial environments. This diminished activity may be attributed to the upregulation of immune suppressive signals, such as PD-1 and CTLA-4. Notably, this process presents a potential target for enhancement through ICIs. Blocking PD-1 could cause immune cells to migrate to the brain and interact with the BBB by producing factors such as IFN- γ [11,20].

In addition to the specific cell subpopulations discussed above, hypoxia is a condition consistently present in cancer, including LC, and is associated with carcinogenesis and possibly with the occurrence of metastases [23]. Increasing evidence suggests that hypoxia significantly contributes to cancer dormancy and metabolism. It enhances stem cell activity, facilitating cancer initiation and progression. Hypoxia activates the hypoxia inducible factor (HIF) by silencing the RAS/RAF/MEK/ERK pathway. Recent studies evaluated the link between the presence of HIF and cancer growth. It seems that this factor promotes angiogenesis and other changes in the metabolism of cancer cells, resulting in oncogenesis. In fact, it appears that it is related to the formation of BMs in LC [24]. There are three types of HIF. HIF-1 is a potential therapeutic target in NSCLC, offering a pathway to prevent cancer spread and improve patient prognosis [23].

The greatest limitation in these studies is the small number of patients participating, as it requires both metastasectomy and LC surgery and simultaneous analysis of the samples, making it difficult to execute. In addition, the methods used for their research were not the same, nor were the biomarkers evaluated.

Thus, despite significant heterogeneity between primary lung tumors and their corresponding BMs, patients may derive therapeutic benefits from ICI treatment, given the activation observed in both intracranial and extracranial immune systems.

Single-agent anti-programmed death-ligand 1/ programmed cell death protein 1 or anti-cytotoxic T-lymphocyte antigen 4 monoclonal antibodies

A non-randomized, open-label phase 2 trial enrolled 18 patients with melanoma and untreated BMs and 18 patients with NSCLC plus untreated or progressing BMs plus positive PD-L1 (PD-L1>1%) and established the activity and safety of pembrolizumab, a PD-1 inhibitor, in the CNS. The trial reached the primary endpoint, which was the BM response, as 22% [95% confidence interval (CI): 7-48] of patients with melanoma and 33% (95% CI: 14-59) of patients with NSCLC responded, and the CNS response was durable [25]. Even though this study includes patients with melanoma and only a small number with LC, it is noteworthy as it is the first to evaluate the role of immunotherapy in patients with untreated BMs.

The updated results from the NSCLC arm of the previous trial showed a CNS response in the cohort with PD-L1 expression $\geq 1\%$ [29.7% (95% CI: 15.9-47.0%)] with an intracranial response's duration of 5.7 months (interquartile range: 4.0 to 17.7 months) and with no intracranial response in the PD-L1 negative cohort [26].

This was the first prospective study to demonstrate the efficacy

cy of ICI monotherapy for the management of untreated and asymptomatic BMs.

A pooled analysis of keynote-001, 010, 024, and 042 also tried to retrospectively evaluate the outcomes of pembrolizumab monotherapy in patients with PD-L1-positive NSCLC and previously treated, stable BMs vs. chemotherapy [27]. The median OS in patients receiving pembrolizumab with BM and PD-L1 $\text{TPS} \geq 50\%$ was 19.7 months (95% CI: 12.1-31.4) with a hazard ratio (HR) of 0.67 (95% CI: 0.44-1.02). Similarly, benefit was achieved in the PD-L1 $\text{TPS} \geq 1\%$, where the OS was 13.4 months (95% CI: 10.4-18.0) with a HR of 0.83 (95% CI: 0.62-1.10). In both cohorts, the activity of pembrolizumab was higher than in the chemotherapy arm; however, patients with PD-L1 $\geq 50\%$ had even greater benefit than those with PD-L1 $\text{TPS} \geq 1\%$. The safety profile of pembrolizumab was more favorable than that of chemotherapy, and the presence of BMs did not affect the incidence of adverse events (AEs).

The phase III open-label OAK study evaluated the effectiveness and safety of atezolizumab vs. docetaxel as a second-line treatment in patients with PD-L1-unselected advanced or metastatic NSCLC [28]. Atezolizumab is an anti-PD-L1 monoclonal antibody approved for the treatment of metastatic NSCLC with disease progression.

Using data from the OAK trial, Gadgeel *et al.* performed a detailed analysis, particularly for the patients with advanced NSCLC and asymptomatic, previously treated from BMs, highlighting the benefit of atezolizumab in OS, providing a longer period until the appearance of new symptomatic brain lesions and fewer AEs compared to docetaxel [29].

Another ICI of this category is nivolumab. The superiority of nivolumab over docetaxel as second-line treatment in patients with advanced squamous and non-squamous NSCLC has already been established by 2 phase III studies [30,31]. Various studies based on the nivolumab Italian Expanded Access Program examined the subgroup of patients with CNS metastases. The studies involved patients with disease progression or recurrence after systemic therapy and treated metastatic CNS lesions [32,33]. The median progression-free-survival (PFS) for the squamous NSCLC was 4.9 months (95% CI: 2.7-7.1), and the OS was 5.8 months (95% CI: 1.8-9.8) while for the non-squamous NSCLC it was 3 (95% CI: 2.7-3.3) and 8.6 (95% CI: 6.4-10.8) months, respectively.

All these findings were consistent with previous trials, emphasizing that BMs have similar benefits from anti-PD-L1 therapy as the extra-cerebral disease [27,29,32-34]. The ICIs have an acceptable safety profile in advanced and metastatic NSCLC patients, and their efficacy in the subgroup of patients with BMs is comparable to their efficacy in patients without a history of BMs.

The most important limitation is that the majority of these studies refer to stable and asymptomatic metastatic lesions, usually pretreated. Consequently, the true efficacy of these molecules in treating BMs cannot be truly determined. However, the encouraging rates analyzed above show that immunotherapy, even as monotherapy, compared to chemotherapy, is an effective therapeutic option for advanced NSCLC with BMs.

Combined immunotherapy

Due to the fact that ICI monotherapy could benefit NSCLC patients with BMs, numerous scientific groups have investigated whether combining immunotherapy agents can provide a better outcome in this group of patients. The different ICIs have different but complementary mechanisms of action. Although all ICIs contribute

to removing immune system restraints, the specific pathways for restoring anti-tumor immunity are peculiar [11]. Nevertheless, data about ICI combinations in NSCLC with BMs is limited.

In Part 1a of the CheckMate 227 trial [35], 1189 patients with stage IV NSCLC and PD-L1 expression level of 1% or more were enrolled and randomized to receive first-line treatment with ICI combination with nivolumab plus ipilimumab, a fully human CTLA-4 antibody, nivolumab alone, or histology-driven chemotherapy. 202 patients had baseline BMs. The study achieved its primary endpoint by demonstrating that double immunotherapy was superior in terms of OS compared to chemotherapy alone ($p=0.007$, $\text{HR}=0.79$).

It is worth mentioning that the OS with nivolumab plus ipilimumab was nearly identical in patients with PD-L1 $\geq 1\%$ and $<1\%$, suggesting that maybe the different immune effects of CTLA-4 inhibition may be important in PD-L1-negative tumors for obtaining antitumor immunity.

The 4-year outcomes from CheckMate 227 reported the durable benefit of dual immunotherapy as a first-line treatment across all efficacy endpoints, regardless of the PD-L1 expression level or tumor histology [36].

A post-hoc analysis specifically for the patients with BMs confirmed the efficacy of double immunotherapy in OS (18.8 vs. 13.7 months in chemotherapy with HR 0.57) and PFS (1y PFS 38% vs. 21% with HR 0.79) and in the duration of response (DOR) (29.9 vs. 8.4 months) [37]. In the same context, the 5-year follow up showed a prolonged OS ($\text{HR}=0.63$; 95% CI: 0.43-0.92), 5-year systemic and intracranial PFS (iPFS) rates at 12% and 16% respectively (0% and 6% respectively for the chemotherapy arm) and fewer incidents of new brain lesions appearance (4% vs. 20% with chemotherapy) [38].

Apart from the encouraging clinical benefit, CheckMate 817 compounded the tolerable safety profile of dual immunotherapy in the special category of patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 and untreated BMs with manageable treatment-related toxicity, similar to the general population [39].

Combination of immunotherapy with chemotherapy

The combination of immunotherapy with systemic therapy is a commonly selected first-line treatment for patients with metastatic NSCLC [9]. While chemotherapy's inability to penetrate the BBB has been noted, ongoing investigations explore the presence of BMs and potential synergistic effects between immunotherapy and chemotherapy. Chemotherapy has demonstrated the ability to enhance the efficacy of ICIs by increasing neoantigen expression, promoting immunogenic cell death, and upregulating PD-L1 expression within the TME. Consequently, this fosters T-cell activation and response [11,40,41].

Keynote 021, 189, and 407 tried to evaluate the efficacy of pembrolizumab plus platinum-based chemotherapy as first-line treatment for metastatic NSCLC compared to chemotherapy alone [42-44]. All these trials permitted enrollment of patients with asymptomatic, pre-treated (Keynote 021) or untreated (Keynote 189 and 407) BMs.

Powell *et al.* executed a pooled analysis of these trials, investigating the efficacy of immunotherapy plus chemotherapy in patients with stable BMs [45]. The superiority of this combination was evident across all endpoints analyzed (OS 18.8 vs. 7.6 months for

chemotherapy alone, PFS 6.9 vs. 4.1 months, objective response rate 39% vs. 19.7%, median duration of response 11.3 vs. 6.8 months). This benefit was consistently observed across all PD-L1 expression subgroups.

Attempting to evaluate the possibility of a faster initial disease control, scientists in CheckMate 9LA added a limited course of chemotherapy (2 cycles) to dual immunotherapy with nivolumab and ipilimumab and found that the combination regimen provided a significant and durable improvement in OS, with a favorable risk-benefit profile [46].

Carbone *et al.* focused on the 101 patients who had stable or asymptomatic BMs and concluded that the patients in the combination arm had a considerable gain in PFS and OS (1-year PFS rate: 36% vs. 8%, 1-year OS rate: 67% vs. 26%) and the benefits were consistent with the ones observed in all randomized patients from CheckMate 9LA [47].

The ATEZO-BRAIN trial, a single-arm phase II study, represents the first investigation into the efficacy of ICIs atezolizumab in combination with platinum-based chemotherapy in 40 patients with non-squamous NSCLC and untreated BMs, a population often excluded from trials [48]. Results showed that the combination therapy had an acceptable safety profile and achieved a 12-week PFS rate of 62.2%. Significantly, it demonstrated comparable efficacy both systemically and intracranially, suggesting the possibility of serving as a therapeutic option for this highly vulnerable patient population. However, this is a single-arm trial, which prevents the establishment of an optimal treatment approach.

Combination of immunotherapy with radiotherapy

Concurrent administration of ICIs with radiotherapy is a crucial area of investigation. It seems that radiation induces cell death and stimulates the production and release of cytokines and chemokines, particularly type I interferons, within the TME [49]. Consequently, cytotoxic T-cells and suppressive cells, like Treg, infiltrate the tumor, while immune cells such as dendritic cells, which play a crucial role in presenting antigens, migrate out of the tumor [50]. Moreover, it can also increase the permeability of the BBB. Thus, it can provide a more active immune microenvironment for ICI treatment [51].

Ikirashi *et al.* compared the microenvironment of the brain in patients who received localized radiation for the metastatic site before surgery, with those who did not receive such treatment [16]. The findings revealed that patients who underwent radiation prior to brain surgery had a higher concentration of TILs within the metastases. Notably, the density of CD4+ T-cells and CD4+Foxp3+ T-cells in the radiation group was statistically higher than in the untreated group, both in the carcinoma and stromal regions.

Since radiation can potentially improve patient outcomes, research has begun to explore whether it can also be used for metastatic LC with BMs, elaborating efficacy and safety.

In a small phase II open-label trial [52], 22 patients with NSCLC and 4 with renal cell carcinoma were submitted in treatment with nivolumab plus SRS, 14 days after the first dose of immunotherapy. The systematic therapy was not the first-line treatment. The study revealed a clinically meaningful improvement in controlling intracranial response with an iPFS rate at 45.2% (95% CI: 29.3-69.6%) at 1 year and a median iPFS of 6.1 months (95% CI: 3.5-NA months), with an intracranial progression

probability of 19.5% (95% CI: 6.5-37.6%) at 1 year. However, the probability of extracranial progression was high (46% at 1 year), suggesting the possibility that the addition of an extra drug to systemic therapy is necessary, as mentioned in the trials above.

Influenced by the positive results of the CheckMate 227 trial and considering patients with untreated BMs, Jing Li *et al.* tested the nivo/ipi combination with concurrent SRS for active [53], untreated or progressive intracranial metastases from NSCLC. The number of patients enrolled was small (13 patients); however, the results both for the intracranial and extracranial responses and for the safety profile of this combination were encouraging.

The advantages of the combination of the two treatments became clearer with the analysis of Chen *et al.* [54], who separated 74 patients with metastatic melanoma and metastatic NSCLC into two groups: one who underwent only radiotherapy (WBRT or SRS) and one who received radiotherapy and ICI treatment. Although patients with melanoma were also included in this study, the encouraging results were noteworthy. Both PFS and OS were significantly higher in the concurrent group, findings in agreement with those reported in other trials. The intracranial disease progression was higher in the monotherapy group, with 93% of patients who received SRS alone having new intracranial metastases compared to 53% in patients who received concurrent immunotherapy ($p=0.0006$, OR 17.14, 95% CI: 2.97-99.1).

The timing of administration of radiation therapy is another factor that needs to be evaluated. So far, the studies mentioned used concurrent radiotherapy and ICI therapy. Schapira *et al.* conducted a retrospective analysis of patients treated with a combination of SRS and PD-1 pathway inhibitors, focusing on the time of administration [55]. Simultaneous administration was associated with a better OS rate compared to SRS before or after the administration of immunotherapy, respectively (1-year OS 87.3% vs. 70.0% vs. 0%, $p=0.008$), and the possibility of new brain lesions' appearance was lower (1-year distant brain failure 38.5% vs. 65.8% vs. 100%, $p=0.042$). No grade 4 or 5 toxicities were observed.

In a multicentric retrospective study, NSCLC patients with BMs treated with radiotherapy and immunotherapy showed longer intracranial local PFS compared to those treated with exclusive radiotherapy. Combined treatment was better tolerated and not associated with increased toxicity or radionecrosis [56].

Overall, there is agreement that the combination of immunotherapy plus radiotherapy is safe, does not increase the incidence of radiation necrosis or neurological side effects, and the complications are as common as immunotherapy alone, with maximum grade 3 and 4 AEs. The different definitions of concurrent therapy used in every study make it difficult to conclude about the time of administration of radiotherapy.

Immunotherapy and targeted therapy

Immunotherapy's efficacy appears to be present in cases of individuals with targetable mutations and BMs, even though they are often excluded from investigations assessing immunotherapy combinations due to guidelines favoring first-line targeted therapies. Intriguingly, tyrosine kinase inhibitors, particularly the newer generations utilized in the management of epidermal growth factor receptor-mutant LC, demonstrate a favorable impact on CNS outcomes [57,58]. However, as a secondary treatment approach, the combination of immunotherapy with chemotherapy has shown superior CNS efficacy compared to chemotherapy alone [59].

Adagrasib, a second-line treatment option in patients with *KRAS* G12C mutation, seems to penetrate the CNS, achieving effective concentrations in the cerebrospinal fluid [60,61]. Given the challenging nature of treating patients with *KRAS* mutations, preliminary findings from ongoing studies suggest that monotherapy with a *KRAS* inhibitor may not be sufficient, advocating for a combination therapy with immunotherapy [62]. A retrospective study examining the impact of *KRAS* mutational status on the efficacy of ICI in patients with NSCLC and BMs concluded that administering immunotherapy in patients and *KRAS* mutations within 90 days of the initial diagnosis significantly enhanced OS compared to patients who did not receive ICI therapy [63].

Brain metastases from small-cell lung cancer and immunotherapy

SCLC has several peculiarities and a different clinical behavior in relation to NSCLC. It is a chemosensitive tumor, characterized by rapid proliferation and expansion. In most cases, it is diagnosed at an extensive stage, usually with BMs. If not present at the initial diagnosis, 80% of patients will develop brain lesions during the course of their disease [1].

There is no clear recommendation regarding the use of PCI at the extensive stage; however, the indication remains in response to the initial treatment in patients with limited-stage disease [4].

It was not until 2019 that immunotherapy was approved for use in SCLC treatment, and this approval was only for the extensive stage. Hence, now the standard of care includes chemo and immunotherapy combinations [4].

The two main clinical trials that contributed to ICI approval were the IMpower 133 and the CASPIAN study [64,65]. They both demonstrated the superiority of anti-PD-L1 input in OS and PFS. However, only the latter included patients with untreated, asymptomatic BMs. More specifically, in the CASPIAN trial, treatment-naïve patients with extensive SCLC were separated into two groups receiving platinum-based chemotherapy and etoposide with or without durvalumab. In a subgroup analysis of outcomes according to the presence of BMs, it was shown that the OS and the PFS benefits of first-line combination therapy were maintained regardless of the presence of brain lesions. This data is consistent with the data mentioned above about NSCLC, supporting the notion that the brain is an immune-privileged site.

Moreover, the CASPIAN study's 3-year OS data continue to show consistent benefits with the use of durvalumab plus chemotherapy, regardless of whether patients had baseline BMs [65].

Another study by Chang *et al.* tried to evaluate the role of additional immunotherapy in patients with extensive-SCLC and BMs, who had already received chemotherapy (at least 4 cycles) and radiotherapy for the BMs [66,67]. The results were promising as OS and iPFS were significantly improved compared to patients who only received chemotherapy and brain radiotherapy (median OS 13.3 vs. 33.4 months, 1-year OS rate was 54% vs. 82%, median iPFS 6.93 vs. 10.7 months). The major limitation of this analysis was that different types of immunotherapies were administered while some patients had undergone PCI before.

In general, it is more difficult to draw any conclusions about SCLC as the data is very limited and many decisions are based on the treating physician's the treating physician's experience.

Discussion

Immunotherapy has emerged as a transformative modality in the management of LC across all stages, significantly altering the treatment landscape of stage IV disease, which historically carries the poorest prognosis [68].

However, identifying reliable biomarkers for predicting the efficacy of immunotherapy, especially in patients with BMs, remains a major challenge. The advent of biomarkers, such as PD-L1 expression and tumor mutational burden (TMB), has facilitated the identification of patients most likely to benefit from immunotherapy, enabling personalized treatment strategies and optimizing therapeutic outcomes. However, inconsistencies in immunohistochemical tests and cut-off points have led to confusion and dissatisfaction within the medical community [68]. Additionally, the biological heterogeneity of PD-L1 expression within tumors further complicates its predictive value [69]. Despite these challenges, studies have shown that the PD-L1 status obtained from core biopsies or fine needle aspirates is generally consistent with outcomes from paired resections, suggesting that analysis of small samples may provide reliable results [70].

It seems that the use of a single parameter as a marker is not enough because, until now, a precise, easy-to-detect, cheap, and capable biomarker has not been identified in the particularly heterogeneous environment of tumors and tumor metastases. Probably, the combination of TIL's concentration and PD-L1 expression is a noteworthy combination.

Liquid biopsy holds significant relevance in clinical practice, offering a non-invasive means of obtaining real-time molecular information for monitoring treatment efficacy and evaluating disease progression [71]. It can also possibly provide early evidence of drug resistance, which is quite often seen in patients receiving immunotherapy. In addition, studies have shown that liquid biopsy, particularly in cerebrospinal fluid and blood, enables molecular characterization of BMs, facilitating the assessment of tumor evolution and its heterogeneity. It allows for the determination of key immune biomarkers such as PD-L1 expression, TMB, and microsatellite instability status [72]. In the same context, a retrospective study investigating the predictive effect of peripheral blood lymphocyte subsets [73] suggests that baseline peripheral blood CD4+CD45RA- T-cell counts can be used as a biomarker to predict the efficacy of ICIs. Similarly, a study held by Shuai Liu *et al.* added the possible value of easier-to-detect markers in the peripheral blood, such as the neutrophil-to-lymphocyte ratio [74].

Circulating tumor cells (CTCs) have an additional important role as prognostic factors in patients with NSCLC. A prospective study by Rossi *et al.* has shown that an increase in their number is associated with poorer prognosis, lower PFS, and OS. In addition, there are published data supporting the ability to detect, among other factors, ALK rearrangements using CTCs. Those scientific efforts to standardize CTC characterization will soon enable routine assays for all LC patients [75].

Administering immunotherapy is associated with various AEs, while the percentage can reach 60%. In the majority, these immune-related AEs (irAEs) are mild and easily treated without discontinuation of the systematic therapy. However, the risk of fatal conditions such as serious pneumonitis is always present [76]. Potential risks associated with the co-administration of agents, such as antibiotics (ATB), corticosteroids, proton pump inhibitors, or vaccinations, that may affect the mechanisms of action of immunotherapy are often not adequately considered as risk factors for the appearance of side effects [77]. In detail, ATB

can negatively impact outcomes in cancer patients receiving ICIs by reducing gut microbiota diversity and eliminating immunogenic bacteria. Until more evidence is available, ATB use during immunotherapy should be carefully evaluated, especially for long or repeated courses, while ensuring necessary treatment for infections. Decision-making is more complicated when it comes to the use of corticosteroids, as they are essential for the treatment of irAEs and for the relief of patients with BMs. Retrospective studies indicate that early corticosteroid use correlates with poor prognosis, even though this association might be influenced by other factors such as high TMB or poor ECOG performance status [76]. However, recent randomized phase III trials suggest that premedication with corticosteroids does not compromise the efficacy of ICIs in chemo-immunotherapy combinations. More prospective studies are needed to determine the impact of corticosteroids at doses above 10 mg daily of prednisone [77].

When selecting immunotherapy regimens for the treatment of LC, particularly in cases involving patients with BMs, it is crucial to bear in mind the occurrence of pseudo-progression. This phenomenon manifests as the enlargement of existing lesions or the emergence of new ones, which may mimic tumor progression. Radiographic follow-up is more commonly utilized to evaluate these conditions; however, biopsy and histopathologic examination remain the gold standard for confirming pseudo-progression [78]. Understanding that movements like these are difficult to perform in everyday clinical practice, published studies suggest that circulating tumor DNA and serum interleukin-8 levels hold promise as biomarkers for predicting pseudo-progression with high sensitivity and specificity, potentially outperforming radiographic methods. Therefore, careful consideration and vigilance are warranted in the assessment of treatment response, necessitating diligent monitoring and accurate interpretation of imaging findings [78].

It is important to mention that most of these trials and protocols used specific criteria to evaluate the tumor's response to ICI treatment. RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria are globally used to assess treatment response in patients under systemic therapy. However, tumors often respond differently to immunotherapy, following unique patterns such as pseudo-progression, which was discussed earlier. Consequently, the traditional RECIST 1.1 criteria may not accurately reflect responses to immunotherapies. To address this issue, iRECIST (immune-RECIST) criteria are employed in many clinical trials and protocols discussed in this review. iRECIST is based on RECIST 1.1 but includes mechanisms for confirming progression to account for atypical responses. When progression is identified based on RECIST 1.1 principles, it is classified as initial unconfirmed progression (iUPD). This requires confirmation through additional examinations that show either a further increase in size or the appearance of new lesions. If the lesions are stable in subsequent examinations, the disease stage remains iUPD, and it is up to the doctor in charge to decide how to proceed. If there is tumor shrinkage, the situation is classified as complete response, partial response, or stable disease, depending on the specific characteristics. This approach helps differentiate true progression from temporary increases in tumor size or new lesions due to immune response dynamics [79].

The primary limitation of this review, as well as the broader discussion surrounding the utilization of immunotherapy in patients with LC and concurrent BMs, lies in the underrepresentation or outright exclusion of this particular patient demographic from clinical trials. Consequently, the available data remains sparse. Even within the clinical trials that have included individu-

als with active BMs, eligibility criteria often permit the enrollment of patients with pretreated BMs or those undergoing concurrent corticosteroid therapy. This gap between the controlled environment of clinical trials and the real-world clinical setting underscores the necessity for further research and randomized controlled studies to better guide clinical decision-making and optimize treatment strategies for LC patients with active BMs. Furthermore, it is imperative that research endeavors focus on investigating the potential protective role of adjuvant immunotherapy in mitigating the onset of future BMs. Overall, the era of immunotherapy has arrived for LC; however, there are several questions that need to be answered in order to benefit from it in the best way possible.

Conclusions

Most studies support, with significant superiority, the use of immunotherapy-based combination therapy in patients with BMs. There is uncertainty concerning patients with active, symptomatic metastases as they are underrepresented in clinical trials; however, there are several ongoing trials that could provide important answers in the near future. So far, loco-regional therapy stands as the treatment of choice for those patients, with several factors like age, performance status, the number of CNS lesions, and the presence of symptoms guiding method selection. The type of cancer and the existence of targetable mutations can also influence treatment, and a combination of treatments is often required for optimal results. It is evident from this discussion that the issue is highly complex. More prospective trials are required to establish a more definitive and comprehensive therapeutic approach for the management of BMs.

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