Immune checkpoint inhibition in patients with brain metastases

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Metastatic brain tumors are the most common type of central nervous system (CNS) malignancies in adults, outnumbering primary CNS tumors by approximately 10:1 (1). The most common source of brain metastases is non-small cell lung cancer (NSCLC), representing about half of all cases, followed by breast, melanoma, renal, and colorectal cancers (2). While melanoma accounts for only 5% to 10% of metastatic lesions, it has the highest predilection to metastasize to the CNS (3). Although whole brain radiotherapy (WBRT) remains the mainstay for treatment of metastatic CNS lesions, surgical resection and stereotactic radiosurgery are options for patients with amenable lesions. Small molecule inhibitors targeting disease-associated driver mutations such as *BRAF* inhibitors in melanoma, and *EGFR* or *ALK* inhibitors in NSCLC have shown efficacy in controlling intracranial disease. Nevertheless, the eventual development of drug resistance and the large number of patients without actionable mutations makes new therapeutic options necessary. To this end, immunotherapeutic strategies hold significant promise, particularly since such approaches have significantly impacted outcomes in patients with advanced systemic disease for both melanoma and NSCLC (4).

The immune system has inherent immunosuppressive mechanisms, or checkpoints, that have evolved to limit prolonged immune activation and inflammation that would be detrimental to the host. Tumors have co-opted these endogenous mechanisms as a means to evade immunosurveillance by the host immune system. The success of novel therapeutic strategies designed to inhibit these checkpoint pathways leading to a reinvigorated anti-tumor immune response has resulted in a new treatment paradigm in oncology. The first checkpoint pathway targeted clinically was CTLA-4, an inhibitory member of the B7 family of co-regulatory molecules. CTLA-4 is constitutively expressed on the regulatory subset of helper CD4 T cells, and can also be transiently expressed on activated T cells. CTLA-4 binds to the co-stimulatory molecules, CD80 and CD86, expressed on antigen-presenting cells and exerts its immunosuppressive effects in the lymph nodes by limiting the priming and expansion of antigen-specific T cells (5). In contrast, PD-1, another inhibitory B7 family member that is expressed on activated T cells, interacts with its ligands, PD-L1 and PD-L2, in the tumor microenvironment. Binding of PD-1 with either PD-L1 or PD-L2, which are expressed by other tumor-infiltrating immune cells as well as some tumor cells, leads to an "exhausted" phenotype characterized by decreased effector function and proliferative capabilities. While there is a growing list of immune checkpoints being investigated as potential therapeutic targets, the currently approved drugs are inhibitors of CTLA-4 and the PD-1/PD-L1 axis.

In melanoma, the first approved checkpoint inhibitor was ipilimumab, an antagonistic monoclonal antibody specific to CTLA-4. In a randomized trial comparing ipilimumab to the gp100 vaccine or the combination, the median overall survival (OS) for patients receiving ipilimumab either alone or with vaccination was approximately 10 months compared to 6.4 months for vaccination alone (P<0.001) months (6). Subsequently, the anti-PD-1 antibodies nivolumab and pembrolizumab were approved based on the results from two phase III trials. In the Checkmate-066 trial (7), 418 patients were randomized to nivolumab 3 mg/kg every 3 weeks or dacarbazine. Nivolumab was associated with improved ORR (40.0% *vs.* 13.9%, P<0.01), median PFS (5.1 *vs.* 2.1 months, P<0.001) and 12-month OS (72.9% *vs.* 42.1%, P<0.001). In the Keynote-006 (8), 834 patients were randomized to pembrolizumab 10 mg/kg every 2 weeks,

pembrolizumab 10 mg/kg every 3 weeks or ipilimumab 3 mg/kg every 3 weeks. The two pembrolizumab arms were associated with a significant improvement in ORR (33.7% and 32.9% *vs*. 11.9%, P<0.001 for either pembrolizumab arm *vs*. ipilimumab) and 12-month OS (74.1% and 68.4% *vs*. 58.2%, P<0.001 for either pembrolizumab arms *vs*. ipilimumab).

In NSCLC, both nivolumab and pembrolizumab have been approved based on three large randomized phase III studies comparing either nivolumab or pembrolizumab to docetaxel in patients with previously treated disease (9-11). In each of these studies, PD-1 blockade resulted in a significant improvement in median OS compared to docetaxel. Recently, Atezolizumab, an anti-PD-L1 antibody, demonstrated similar improvements in median OS and response rate compared to docetaxel in patients with previously treated NSCLC suggesting that blocking either member of the PD-1/PD-L1 axis results in similar clinical benefit (12).

Patients with brain metastases were mostly excluded from the randomized trials unless the lesions were asymptomatic, previously treated, and documented stable prior to enrollment, with few exceptions. Therefore, due to the small number patients with known active CNS disease enrolled in these trials, no meaningful conclusions could be inferred regarding the impact of checkpoint blockade on intracranial disease, and the efficacy of systemic immune reactivation by checkpoint blockade therapy in controlling CNS disease remains unknown.

The preliminary support for a possible role of checkpoint blockade in treating active brain metastases has been provided by anecdotal case reports of patients with metastatic melanoma treated with ipilimumab (13,14). Subsequently, several retrospective analyses of phase II and III clinical trials of ipilimumab in the treatment of metastatic melanoma reported an overall disease control rate (DCR) of 16% to 27% in patients with stable CNS disease (15,16). These data lead to a prospective phase II study examining the efficacy of ipilimumab in patients with metastatic melanoma and untreated or progressive brain lesions (17). Two cohorts were enrolled to assess the response in asymptomatic lesions and symptomatic lesions requiring corticosteroids to control clinical symptoms. The CNS DCRs were 24% (12/51) and 10% (2/21), respectively. While these data are limited to patients with metastatic melanoma and CTLA-4 blockade, given the improved responses and efficacy in both melanoma as well as NSCLC, it would be reasonable to hypothesize that PD-1/PD-L1 blockade may also have a positive impact on intracranial disease. Indeed, in a recent retrospective analysis of five patients with new or progressing brain metastases from NSCLC treated with PD-1 blockade, an objective response was observed in two patients and persisted for greater than 6 months, suggesting a possible role for anti-PD-1 therapy in treating CNS metastases (18).

In the first prospective study evaluating the role of anti-PD-1 antibodies in patients with brain metastases from melanoma or NSCLC, Goldberg and colleagues (19) reported the preliminary analysis including 18 patients with each malignancy and brain metastases treated with pembrolizumab 10 mg/kg every 2 weeks. The primary endpoint was ORR in the brain metastases, which was observed in 22% of melanoma patients and 33% of NSCLC patients, with the latter including four complete responses. The systemic ORR was also 22% in melanoma and 33% in NSCLC.

While these findings are very encouraging, there are some important considerations to take into account when interpreting these initial results. It should be noticed that based on the inclusion criteria, the enrolled patients represent a highly selected group. While there was no limitation on the number of absolute brain metastases per patient allowed, the size criteria between 0.5 and 2 cm and the exclusion of patients with symptomatic brain lesions, leptomeningeal disease or use of corticosteroids, would make only a small percentage of patients with brain metastases eligible and limit a broad applicability of the findings.

Although the time between brain radiation and initiation of pembrolizumab is not described in the study, it would be interesting to follow patients who had radiation therapy shortly before starting the checkpoint inhibition, to evaluate for toxicity and also the possibility to generate an abscopal effect induced by the radiotherapy. Although none of the patients with target lesions growing after previous irradiation responded, the numbers are still too small and the interval between the radiotherapy and initiation of pembrolizumab may be important. Furthermore, the differences between immunostimulatory and immunosuppressive cancer cell death induced by the radiation therapy may impact the sequence of local and systemic therapy.

The study required that patients with NSCLC had positive PD-L1 expression defined as more than 1% staining by immunohistochemistry and obtained after the most recent systemic therapy. The strong concordance between the systemic and intracranial responses suggest that both may respond in cases of PD-L1 positive tumors.

Nevertheless, since the tissue was obtained from any disease site, the concordance between PD-L1 expression in the extra-cranial and CNS metastases as well as the predictive value of PD-L1 expression in the brain remains unclear.

Overall, the results presented by Goldberg and colleagues suggest that pembrolizumab is an active therapy in selected patients with brain metastases from melanoma or NSCLC, with similar intra-cranial and systemic response rates. Based on the acceptable safety profile from pembrolizumab in patients with CNS metastases and established systemic benefit from immune checkpoint inhibitors even in patients with PD-L1 negative tumors (10,20), it may be worth testing either anti-PD-1 antibody in patients with PD-L1 negative or unknown, particularly in cases without additional local therapy options. It may also be interesting to evaluate the role of immune checkpoint combinations, which have been shown to be more effective than single agent nivolumab or ipilimumab in patients with PD-L1 negative melanoma and possibly NSCLC (21,22). In summary, the preliminary results are very encouraging and should lead to a new treatment approach in this patient population that is often overlooked in clinical trials and for which there are limited systemic therapy options.

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Footnote

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