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Clinical Case Seminar A6(1-9)

Challenges with anti-PD1 agents in brain metastases management of NSCLC patients: a case report

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Abstract

Immunotherapy is dramatically changing the therapeutic landscape of advanced Non Small Cell Lung Cancer (NSCLC), with unprecedented results compared with chemotherapy. However, this novel treatment approach poses several novel challenges, including optimal treatment duration, coexistence with other conventional therapies (radiotherapy, targeted therapies, and chemotherapy), and activity in special populations, including patients with brain metastases (BMs). Traditionally, central nervous system (CNS) has been considered an immune-privileged organ, although recent evidences suggest a potential role of the immune system as exploitable target for cancer immunotherapy. Here we present a case of a non-squamous NSCLC patient with a rapid and long-lasting response to the anti-PD1 agent Nivolumab with a remarkable activity in the CNS, without previous brain irradiation.

KeyWords: NSCLC, Brain Metastasis, Nivolumab, Immunotherapy, Lung Cancer

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Introduction

Immune checkpoint blockage represents a major breakthrough in the rapidly evolving therapeutic landscape of advanced Non Small Cell Lung Cancer (NSCLC). Since the first clinical demonstration of activity of nivolumab in NSCLC (1), anti-PD1/PD-L1 inhibitors are reshaping the therapeutic armamentarium of NSCLC with proved efficacy in both pre-treated (2-5) and chemotherapy-naïve patients (6). However, the advent of this novel class of anticancer agents poses several novel therapeutic challenges. Indeed, in contrast with conventional antineoplastic agents, immunotherapy is associated with lower response rates, but highly durable tumor responses (7), resulting in a long-term survival only in a minority of patients (~15-20% in unselected patients) (8, 9). Hence, it is not surprisingly that optimal treatment duration and adequate patients selection are two of the most important issues with these agents. Moreover, treatment of selected patients populations, commonly excluded from most of the randomized trials evaluating anti-PD1/PD-L1 agents, such as those with brain metastases (BMs), is an emerging challenge, given the relatively high incidence of BMs in NSCLC, with an estimated incidence of ~40% during the course of the disease (10, 11). BMs from NSCLC represent a largely unmet medical need, with limited therapeutic options and a poor prognosis. Traditionally, systemic treatments have been thought

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ineffective against BMs, due to the presence of blood-brain-barrier, and loco-regional therapy (surgery and/or radiotherapy) has been the mainstay treatment in this setting. Moreover, patients with brain metastases are commonly excluded from most randomized trials, limiting the evidence available regarding the intra-cerebral activity of novel anticancer agents, including immune checkpoint inhibitors. In addition, patients responding to immunotherapy may present higher long-term survival rate compared with those treated with conventional chemotherapy and therefore the long-term effects of loco-regional treatments for brain metastases, such as stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT), should not be underestimated. Similarly to oncogene-addicted tumors (12), the therapeutic management of BMs may include in selected cases upfront immunotherapy, delay the use of radiation therapy, avoiding unnecessary toxicity.

Herein, starting from a clinical case of our clinical practice, we would explore the emerging therapeutic challenges in advanced NSCLC the immunotherapy era, focusing on the role of anti-PD1 agents against BMs.

Case presentation

In February 2015, a 68-years old, male, former smoker (50 packs of cigarettes/year), patient referred to our Institution with a clinical suspicion of malignant spinal cord compression. He was suffering for ~ 3 months from progressively more severe back pain and right lower limb paresthesia, followed thereafter by functional deficit. He has no relevant comorbidities, with the exception of a diabetes mellitus type 2 in treatment with metformin, and standard routine laboratory tests and pulmonary function tests were within normal ranges. Therefore, he underwent a lumbar laminectomy surgery of L3-L4 with stabilization of the column, with rapid symptoms relief. The pathology report revealed a bone metastasis from lung adenocarcinoma (TTF1+, p63-), with an EGFR mutational status wild type. No other bio-molecular tests (ALK/ROS1/PD-L1) could be performed. After adequate recovery and post-operative radiotherapy treatment (8 Gy in a single fraction), the patient started in March 2015 1st line treatment with carboplatin/pemetrexed at standard doses for 4 courses, with stable disease (SD), and then pemetrexed maintenance for only 1 cycle, because of low hematological tolerance (anemia G3, thrombocytopenia G4). Concomitant zoledronic acid 4 mg i.v. every 4 weeks was also started. Unfortunately, on November 2015, the patient eventually progressed (**Fig. 1**), with emergence of pleural effusion, enlargement of lung lesions, and emergence of a single brain metastasis of 13 mm, asymptomatic. Concomitantly, the patient experienced a deterioration of clinical conditions (ECOG PS2). Based on the clinic-pathological characteristics, age, performance status and tumor histology, we started in December 2015 2nd line treatment with nivolumab 3 mg/kq i.v. every 2 weeks, while continuing zoledronic acid. The patient experienced a rapid improvement of clinical conditions (ECOG PS 2 → 0), with a partial response at the first radiological evaluation (after 8 weeks) (**Fig. 2**), with a > 30% reduction of the size of primary tumor and brain lesion, disappearance of pleural effusion and bilateral lung metastases, and stabilization of bone and adrenal metastases. Subsequent CT scans performed every 12 weeks showed a SD, accompanied by a progressive reduction of the primary tumor (**Fig. 2**). On February 2018, the patient is still on treatment

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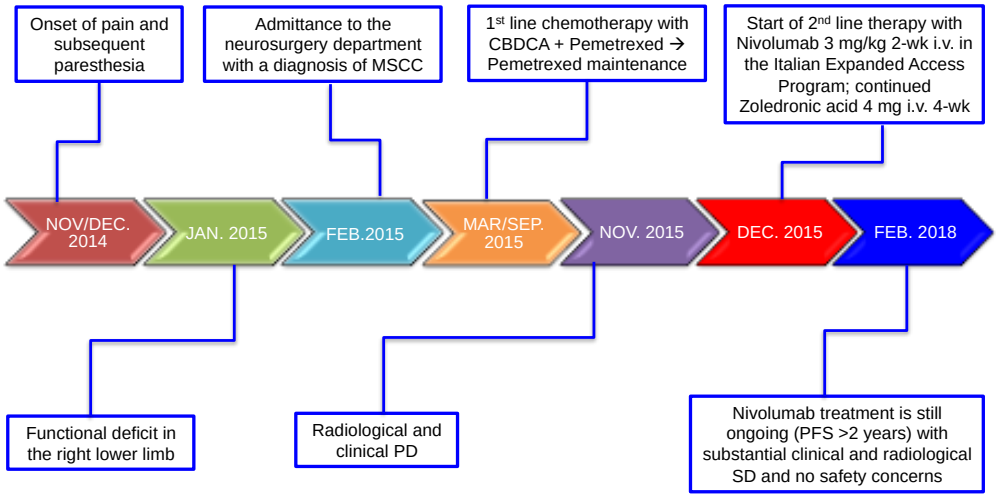
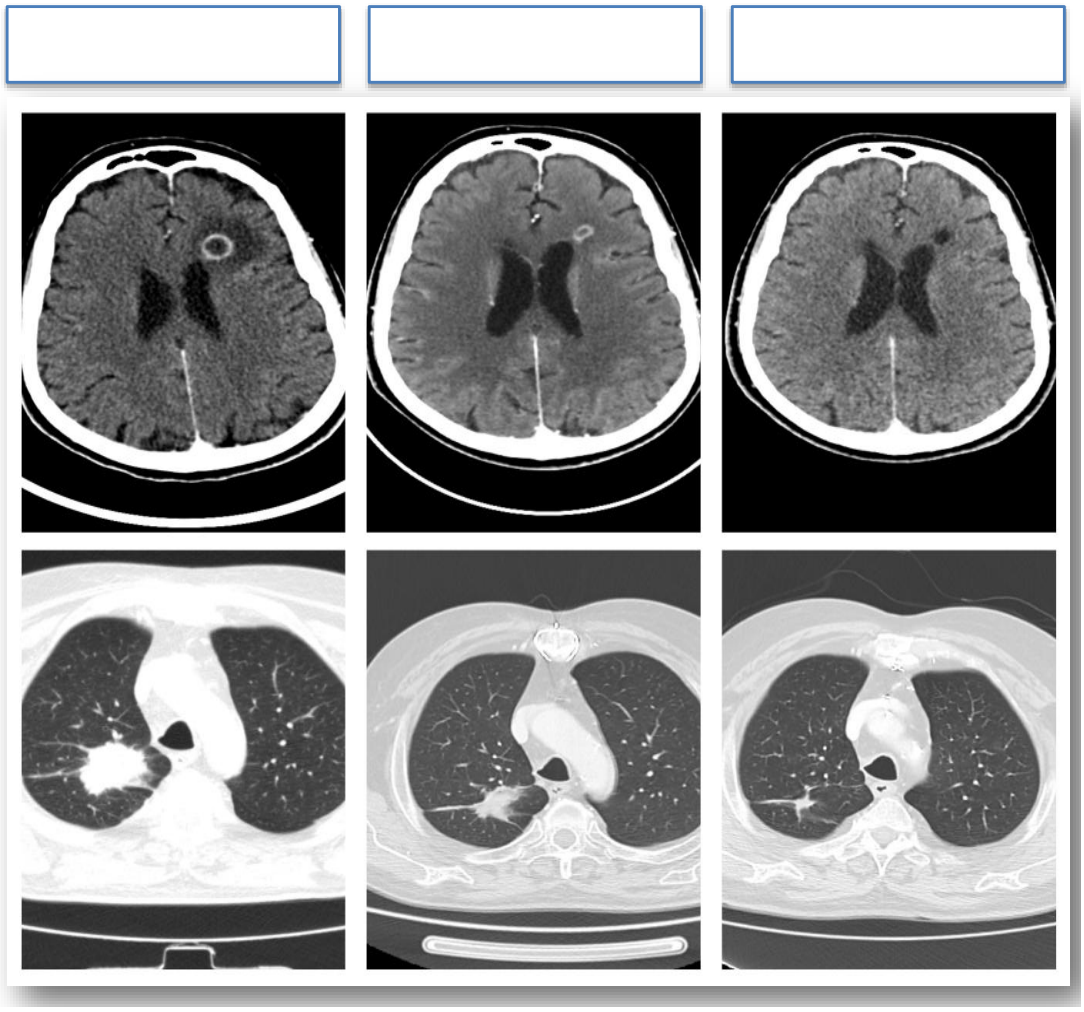
with no relevant toxicities and a good performance status.

Figure 1. Timeline of the clinical course of our patient.



Legend: *MSCC, Malignant Spinal Cord Compression; PD, Progressive Disease; CBDCA, Carboplatin; PFS, Progression-free Survival; SD, Stable Disease.*

Figure 2. Response to nivolumab treatment over time in the primary tumor and in the brain lesion.



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Discussion

Immunotherapy is a firmly established option in the therapeutic armamentarium of NSCLC with three different agents FDA-approved (nivolumab, pembrolizumab, and atezolizumab) in pre-treated patients and one in the first line setting (pembrolizumab), in PD-L1-selected patients. Several important questions still remain unanswered, including optimal treatment duration in non-progressive patients and activity in special populations, such as patients with CNS involvement.

The use of immunotherapy has been traditionally associated with low response rates, but highly durable responses (7) and NSCLC is no exception, with long-term survivors in ~15-20% of the cases (8, 9). However, it is unclear whether responses in these patients could be maintained even upon suspension of the treatment after 1-2 years. Recently, the exploratory analysis of the randomized phase III trial CheckMate-153 were presented, suggesting that treatment discontinuation after 1 year of nivolumab therapy may be inferior to the conventional strategy of continuing until progressive disease and/or unacceptable toxicity both in terms of PFS and OS, independently of the response obtained (13). However, this was only an exploratory analysis of a trial designed to evaluate the safety of nivolumab and the two randomized arms of the study were not stratified according to treatment response (CR/PR vs. SD), making difficult to draw definitive conclusions on the optimal treatment duration of anti-PD1 blockage in pre-treated NSCLC.

Anti-PD1/PDL1 agents have been demonstrated to have an overall better safety profile compared with chemotherapy in NSCLC (14) and immune-related adverse events are usually observed in a small fraction of patients (~10%), most commonly of grade 1-2 (15).

As reported in the present case, long-term treatment with nivolumab is well tolerated, with no safety concerns (9).

The activity of novel therapeutic agents against BMs is always difficult to evaluate, since these patients are often excluded from most of the randomized trials. CNS has been traditionally considered an immuno-privileged organ, with no lymphatic vessels. However, recent insights into the molecular biology of CNS revealed that functional lymphatic vessels lining the dural sinuses can be found and are able to carry both fluid and immune cells from the cerebrospinal fluid, in connection to the deep cervical lymph nodes (16). Moreover, some authors have reported a possible prognostic role of tumor-infiltrating lymphocytes (TILs) in brain metastases from solid tumors (17), suggesting the immune system as a potential exploitable target also for CNS-involving tumors. Moreover, accumulating evidence suggest the potential use of immune checkpoint inhibitors (ICIs) in NSCLC patients with BMs, providing the rationale for further evaluation in the context of clinical trials (18). The first randomized study evaluating the role of

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an ICI in patients with small asymptomatic radiotherapy-naive BMs or progressive radiotherapy-pretreated BMs was a single center phase II trial with pembrolizumab in melanoma and NSCLC patients. Pembrolizumab showed significant activity in patients with untreated or progressive BMs (5-20 mm in diameter without associated neurological symptoms or the need for corticosteroids) from melanoma or NSCLC with an intracranial overall response rate of 22% and 33%, respectively, and an acceptable safety profile (19). In addition, several retrospective studies suggest a potential intracranial activity of anti-PD1/PD-L1 agents in BMs from NSCLC either alone (20, 21) or in combination with SRS (22). Moreover, efficacy of nivolumab seems not influenced by the presence of BMs, with similar survival data between patients with or without BMs at baseline, as reported in two large real-world studies (23, 24).

Data on patients with active BMs (new or growing metastases) are scarce. A recent retrospective study evaluated the activity of nivolumab in patients with brain metastases from NSCLC, including patients with active BMs, and reported similar intracranial and extracranial ORR (9% and 11%, respectively) (25).

As reported here, treatment of small asymptomatic BMs may consider the upfront use of ICIs, delaying the use of loco-regional treatments at neurological symptoms onset or radiologic progression. This strategy may prevent late-term neurological toxicities observed after radiation therapy, given the relatively extended overall survival of these patients.

However, the use radiation therapy in these patients may be associated with improved loco-regional control and longer survival (26, 27) and may have a synergistic effect. Some studies have in fact demonstrated that radiation therapy may alter the permeability of the blood-brain-barrier (25) and may increase the expression of PD-L1 in BMs (29), with a relatively safe neurotoxicity profile (30). On the other hand, some authors have suggested that immunotherapy may increase the risk of radiation necrosis after SRS compared with those who receive chemotherapy or targeted therapies alone (31), as well as peculiar radiologic findings highly suspicious for tumor progression, as a consequence of an accelerated response to SRS treatment (32). Several clinical trials evaluating different combinations are ongoing and will provide definitive conclusions on the optimal treatment strategy in patients with CNS involvement.

Deregulating cellular energetics is a hallmark of cancer (33) and the absence of inhibitory tumor metabolism is one of the seven parameters of the so-called "*cancer immunogram*" that characterize aspects of cancer-immune interactions (34). Recently, a preclinical work suggested a possible interaction between anti-PD1 blockage and metformin. Metformin has the ability to inhibit oxygen consumption in tumor cells, resulting in reduced intra-tumor hypoxia, which in turn acts as a barrier to immunotherapy (35). Therefore, remodeling the hypoxic tumor

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microenvironment might convert "*cold*" tumors in "*hot*" tumors, allowing response to immunotherapy.

In our case, the patient received concomitant oral metformin, because of diabetes mellitus type 2. Therefore, the concomitant use of this hypoglycemic agent might have increased the tumor microenvironment sensibility to immune checkpoint blockage of nivolumab. These data should further evaluated prospectively.

Conclusions

The present case further supports the clinical activity of nivolumab in patients with CNS involvement, confirming the relatively favorable safety profile, even in long-term responders. The good intracranial activity of this agent and the relatively longer overall survival of these patients suggest a possible upfront use for small asymptomatic BMs, delaying the recourse of loco-regional treatments (SRS and/or WBRT) as salvage therapies in case of CNS progression. However, several important questions still remain unanswered. To date, no data have been reported regarding the CNS penetration of ICIs and the cerebrospinal fluid concentrations of these drugs are largely unknown. Moreover, predictive biomarkers are still lacking and pseudo-progression may represent an important issue in patients with BMs, especially after loco-regional therapies.

Further prospective studies are needed to draw definitive conclusions on the role of ICIs in BMs from NSCLC and to define the optimal therapeutic strategy in these patients.

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