CASE REPORT

Combination of Atezolizumab, Bevacizumab, and Chemotherapy (IMpower 150) in a Patient With NSCLC Having Leptomeningeal Metastases

Jordi Remon, MD,[a,*] María Castro-Henriques,[a] Laura Esteller,[a] Josep Vives[b]

[a]*Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona, Spain*
[b]*Department of Radiology, Hospital HM Delfos, HM Hospitales, Barcelona, Spain*

Received 18 June 2020; revised 22 August 2020; accepted 5 September 2020
Available online - 12 September 2020

Introduction

Leptomeningeal metastases (LMs) occur in 3% to 9% of NSCLC cases, with a limited survival (~3 mo) in patients with wild-type NSCLC, and up to 12 months for patients with a targetable genomic alteration.[1] Therefore, there is a clinical need for identifying new therapies for these patients with LM.

Clinical Case Report

A 73-year-old, former smoker, male patient was diagnosed in 2013 with lung adenocarcinoma (pT1a N0 M0). In August 2019, brain magnetic resonance imaging (MRI) was performed, which revealed three brain metastases (BMs) lesions without extracranial progression in positron emission tomography scan. Pathologic analysis from the biopsy of the BM reported metastatic adenocarcinoma from the primary lung cancer. Next-generation sequencing (Oncomine comprehensive assay version 3) of the BM lesions was done and was found to be positive for *KRAS* G12V mutation, with a tumor mutational burden of 9.3 mutations per megabase. Programmed death-ligand 1 (clone 22C3) was found to be expressed in 3% of tumor cells. As the brain was a unique site of relapse, the patient received intensity-modulated radiation therapy (27 Gy in three fractions) without systemic treatment.

After 2 months, the patient complained of painful bilateral L4 radiculopathy. Bone scintigraphy, whole-body computed tomography scan, and brain MRI were performed, which did not find evidence of progression; pain medications were then started (nonsteroidal anti-inflammatory drugs and pregabalin). At 5 weeks, the symptoms had not improved; thus, a new brain and total spine MRI was done, which confirmed both the progression of brain lesions and micronodular LM (Fig. 1) without extracranial disease. LM was also confirmed by means of a positive cerebrospinal fluid (CSF) cytology. The patient was taken off steroids, had minimal neurologic symptoms, and remained in performance status 0, suggesting a good risk classification of LM. Therefore, in January 2020, the patient was started on a 3-weekly combination of atezolizumab and bevacizumab plus paclitaxel and carboplatin (ABPC). After two cycles, radiologic tests reported a stable disease, although the CSF analysis before each cycle remained positive (Fig. 1). Nevertheless, the patient reported clinical improvement. After 4 cycles, lumbar MRI and CSF analysis revealed a complete radiologic and cytologic response in LM (Fig. 1) with partial response in BM. The patient completed a total of six cycles with a confirmed radiologic and cytologic response, and maintenance treatment is ongoing. Treatment-related adverse events that have been reported included grade 1 asthenia and hypertension.

***Corresponding author.**

***Disclosure:** Dr. Remon reports serving in an advisory board for Boehringer-Ingelheim, Merck Sharp & Dohme, Pfizer, Bristol-Myers Squibb, and AstraZeneca; and has received support for travel from OSE-immunotherapeutic, Bristol-Myers Squibb, and AstraZeneca outside of current work. The remaining authors declare no conflict of interest.*

Address for correspondence: Jordi Remon, MD, Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Avinguda Vallcarca, 151, 08023 Barcelona, Spain. E-mail: jordi.remon@delfos.cat

Cite this article as: Remon J, et al. Combination of Atezolizumab, Bevacizumab, and Chemotherapy (IMpower 150) in a Patient With NSCLC Having Leptomeningeal Metastases. JTO Clin Res Rep 2:100096

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100096

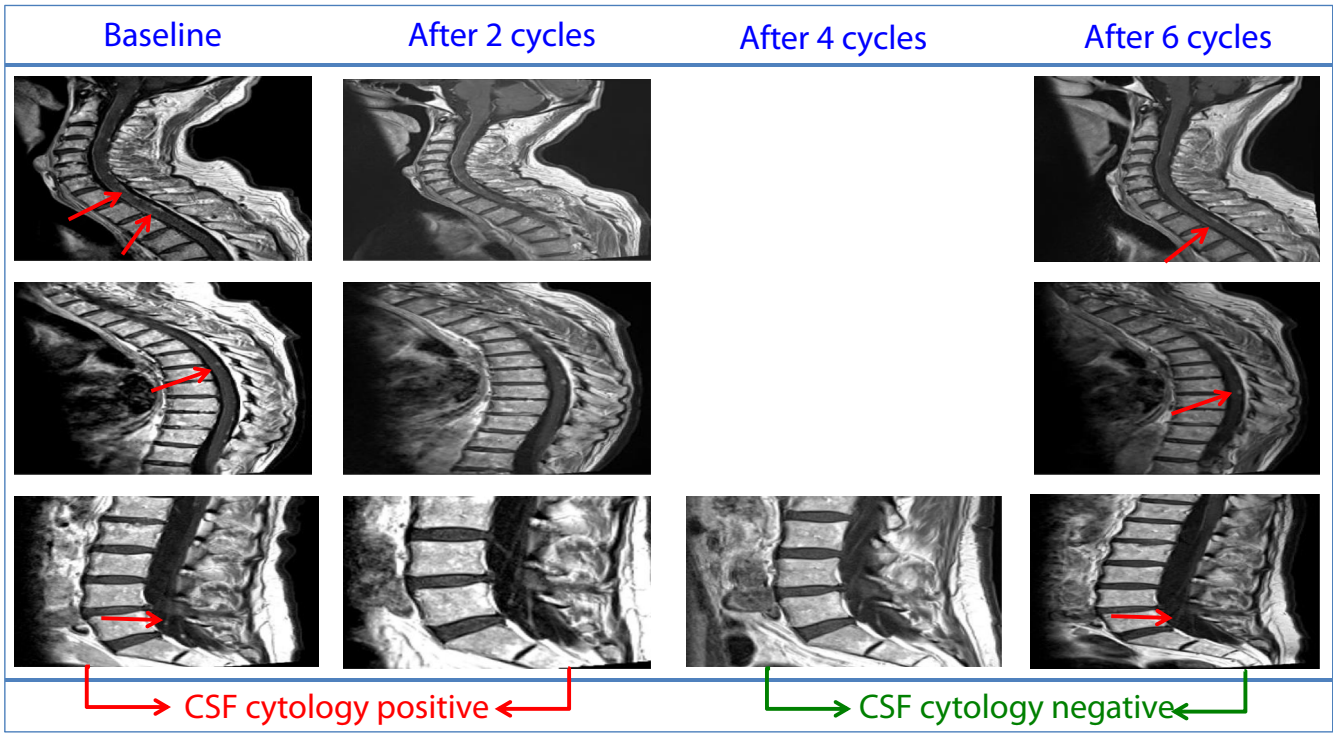

Figure 1. Radiologic assessment of LMs assessed by MRI (red arrow) at baseline and during treatment. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; LM, leptomeningeal metastasis.

Discussion

In NSCLC, upfront immune-chemotherapy combination improves the outcome compared with chemotherapy alone, regardless of *KRAS* status.[2] Recent data from clinical trials suggest that selected patients with NSCLC with BM (asymptomatic and treated, or asymptomatic and small) also benefit from immune checkpoint inhibitors (ICIs) with or without chemotherapy, but the best treatment strategy still needs to be defined.[3,4] Although the efficacy of ABPC is unknown in patients with BM or LM,[5] it is recognized that bevacizumab may prevent BM formation[6] and acts synergistically with ICI,[7] whereas bevacizumab with chemotherapy have reported meaningful clinical efficacy and acceptable safety in patients with BM, suggesting that ABPC may be a reasonable treatment option. Systemic chemotherapy remains the standard of care in the treatment of patients with wild-type NSCLC with LM. The role of bevacizumab in LM is unknown but has been reported to have synergism with chemotherapy in other tumors such as breast cancer.[8] Indeed, a recent retrospective analysis reported that patients with NSCLC with a good-prognosis LM disease (according to the National Comprehensive Cancer Network classification) might obtain benefit from ICI, with a 12-month overall survival of 21%.[1] Therefore, on the basis of all these data, we decided to start ABPC, and the patient achieved radiologic and cytologic response with meaningful clinical benefit and without neurologic adverse effects. Whether programmed death-ligand 1 expression may help to improve patient selection or whether bevacizumab is a cornerstone treatment in LM remains unknown. In addition, the response assessment of LM through imaging remains challenging, especially if prospective clinical trials are launched in this population.[9] To our knowledge, this is the first evidence that intensive treatment in good performance status NSCLC patient with good prognosis, LM may overcome the poor prognosis of this disease.

Acknowledgments

The authors thank the patient involved in this study who gave his informed consent, authorizing the use and disclosure of his health information. Dr. Remon wrote the original draft of the manuscript, whereas Castro-Henriques, Esteller, and Vives contributed to the review and editing of the manuscript.

References

1. Hendriks LEL, Bootsma G, Mourlanette J, et al. Survival of patients with non-small cell lung cancer having leptomeningeal metastases treated with immune checkpoint inhibitors. *Eur J Cancer*. 2019;116:182–189.
2. Gadgeel S, Rodriguez-Abreu D, Felip E, et al. KRAS mutational status and efficacy in KEYNOTE-189: pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. *Ann Oncol*. 2019;30(suppl 11):xi64–xi65.
3. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2020;21:655–663.
4. Henon C, Remon J, Hendriks LE. Combination treatments with immunotherapy in brain metastases patients. *Future Oncol*. 2020;16:1691–1705.
5. Socinski MA, Jotte RM, Cappuzzo F, et al. Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. *J Clin Oncol*. 2018;36(suppl 15):9002.
6. Ilhan-Mutlu A, Osswald M, Liao Y, et al. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther*. 2016;15:702–710.
7. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer*. 2019;18:60.
8. Chen TW, Jan IS, Chang DY, et al. Systemic treatment of breast cancer with leptomeningeal metastases using bevacizumab, etoposide and cisplatin (BEEP regimen) significantly improves overall survival. *J Neurooncol*. 2020;148:165–172.
9. Le Rhun E, Devos P, Boulanger T, et al. The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: lack of feasibility and clinical utility and a revised proposal. *Neuro Oncol*. 2019;21:648–658.