BRIEF REPORT

Atezolizumab-Induced Aseptic Meningitis in Patients with NSCLC

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Received 30 January 2020; revised 31 January 2020; accepted 2 February 2020
Available online - 13 February 2020

ABSTRACT

Introduction: During treatment with immune checkpoint inhibitors, immune-related adverse events sometimes occur, and their management is a critical concern associated with such treatment. Encephalitis and meningitis are some of the critical immune-related adverse events. Atezolizumab is an immune checkpoint inhibitor that inhibits the programmed cell death-ligand. Encephalitis and meningitis were reported in 0.8% of the patients in the atezolizumab versus docetaxel in patients with previously treated NSCLC. However, none of the reports have clarified the details concerning atezolizumab-induced encephalitis and meningitis, including their background, time of onset, treatment, and therapeutic course. We herein report about three patients who experienced atezolizumab-induced meningitis in our department.

Methods: Of the 29 patients who received atezolizumab in our department between October 2015 and September 2018, three developed aseptic meningitis. We retrospectively examined their clinical, radiologic, and cytologic features.

Results: In all three cases, a depressed level of consciousness followed fever in cycle 1, days 15 and 16 after administration of atezolizumab. Cerebrospinal fluid examination revealed that the number of cells was not increased despite the protein level being high. No definite malignant cells were identified in the cerebrospinal fluid in any of the three cases. Only one patient exhibited abnormal enhancement along the lines of the corpus callosum on magnetic resonance imaging. On the basis of these findings, the patients were diagnosed with atezolizumab-induced meningitis. After the administration of methylprednisolone (1000 mg for 3 d), they promptly became conscious and alert.

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Disclosure: Dr. Toyozawa reports receiving personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakka Kirin, MSD, Nippon Boehringer Ingelheim, Nippon Kayaku, Novartis Pharma, Ono Pharmaceutical, and Tai ho Pharmaceutical and grants from Abbvie, Daiichi Sankyo, Pfizer Japan, and Takeda Pharmaceutical outside of the submitted work. Dr. Haratake reports receiving personal fees from Bristol-Myers Squibb, Chugai Pharmaceutical, and MSD outside of the submitted work. Dr. Takamori reports receiving personal fees from AstraZeneca and Chugai Pharmaceutical outside of the submitted work. Dr. Miura reports receiving personal fees from Nippon Boehringer Ingelheim, Ono Pharmaceutical, and Tai ho Pharmaceutical outside of the submitted work. Dr. Yamaguchi reports receiving grants and personal fees from Chugai Pharmaceutical; personal fees from AstraZeneca, Covidien Japan, Daiichi Sankyo, Eli Lilly Japan, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Ono Pharmaceutical, and Tai ho Pharmaceutical; and grants from Pfizer Japan outside of the submitted work. Dr. Takenoyama reports receiving grants and personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Covidien Japan, Eli Lilly Japan, Johnson & Johnson, Kyowa Hakko Kirin, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Ono Pharmaceutical, Pfizer Japan, and Tai ho Pharmaceutical; personal fees from Nippon Kayaku; and grants from KM Biologics outside of the submitted work. Dr. Seto reports receiving grants and personal fees from AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Takeda Pharmaceutical; personal fees from Astellas Pharma, Bristol-Myers Squibb, Kyowa Hakko Kirin, Ono Pharmaceutical, Taiho Pharmaceutical, and Thermo Fisher Scientific; and grants from Abbvie, Sayer Yakuhin, Kissei Pharmaceutical, LOXO Oncology, and Merck Serono outside of the submitted work. The remaining authors declare no conflict of interest.

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Cite this article as: Toyozawa R, et al. Atezolizumab-Induced Aseptic Meningitis in Patients with NSCLC. JTO Clin Res Rep 1:100012

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100012

Conclusion: Atezolizumab-induced meningitis may have some specific features, such as a characteristic development period, findings in magnetic resonance imaging, and premonitory symptoms.

Keywords: irAE; Non–small cell lung cancer; Atezolizumab; Aseptic meningitis

Introduction

Immune checkpoint inhibitors (ICIs), which target the programmed cell death-1 and programmed cell death-ligand 1 (PD-L1) pathways, have been established as a standard of care in the management of NSCLC.[1] Several ICIs, such as nivolumab, pembrolizumab, atezolizumab, and durvalumab, are now available for the treatment of NSCLC.[2-5]

Atezolizumab is a representative of the PD-L1 inhibitors, and its survival superiority to docetaxel, which is the standard therapy, was exhibited in patients with pretreated NSCLC (overall survival: 13.8 vs. 9.6 mo, $p = 0.0003$).[4] On the basis of these study results, atezolizumab has now become the standard therapy for NSCLC.

However, with ICI therapy, immune-related adverse events (irAEs) sometimes occur, and their management is a critical concern.[6] Encephalitis and meningitis are two such irAEs. In the study "Atezolizumab versus docetaxel in patients with previously treated NSCLC" (OAK study), encephalitis and meningitis were found in 0.8% (5 of 609 patients) of the atezolizumab group, whereas in the Japanese population, they are observed in 7.1% (four of 56 patients).[7] However, no reports have clarified the detailed information concerning atezolizumab-induced encephalitis and meningitis, such as the background, time of onset, treatment, and therapeutic course.

We herein report three patients who experienced atezolizumab-induced meningitis in our department.

Methods

Atezolizumab was administered to 29 patients in our department between October 2015 and September 2018. Three of them developed aseptic meningitis induced by atezolizumab. We retrospectively reviewed the symptoms, imaging findings, cytologic findings in cerebrospinal fluid (CSF), and treatment course of these three patients (Table 1).

Results

Case 1

Case 1 was a 71-year-old woman who had been diagnosed with advanced NSCLC, not otherwise specified. Atezolizumab(1200 mg/body, day1) was administered with a cytotoxic agent as the first-line therapy in a clinical trial setting. The tumor proportion score (TPS) of the PD-L1 expression was not mentioned, on the basis of clinical trial protocol guidelines. She developed fever over 38.0°C on day 14 of cycle 1, and her consciousness level was depressed by day 16. Magnetic resonance imaging (MRI) findings did not exhibit any apparent abnormality in the brain. CSF examination revealed that the number of cells was not increased despite the protein level being high (up to 136 mg/dL). Given the lack of definite malignant cells in the CSF, we considered this to be a likely case of drug-induced meningitis caused by atezolizumab use. On day 17, methylprednisolone (1000 mg for 3 d) was started, and she became conscious and alert on day 18 (Table 1).

Case 2

Case 2 was a 55-year-old man, diagnosed through pathologic examination, with nonresectable lung adenocarcinoma with a TPS of 1% to 24%. Cytotoxic agents and ICI or placebos were administered as the first-line treatment in the clinical trial. After four cycles, maintenance therapy was continued. When disease progression occurred, atezolizumab (1200 mg/body, day1) was administered as the second-line therapy. He developed a high fever of over 38.0°C on day 11 of cycle 1, and his level of consciousness was depressed by day 15. There were no apparent abnormalities on brain MRI. CSF examination revealed that the number of cells was not increased despite the protein level being high (up to 130 mg/dL). The cytology of the CSF was class II. Methylprednisolone (1000 mg for 3 d) was started on day 16, on the basis of a possible diagnosis of atezolizumab-induced meningitis. He became conscious and alert at day 18, and his meningitis was then considered to have ameliorated (Table 1).

Case 3

Case 3 was a 50-year-old man who was diagnosed with advanced adenocarcinoma by pathologic examination. The TPS of the PD-L1 expression was 1% to 24%. After three lines of treatment with cytotoxic chemotherapy, atezolizumab(1200 mg/body, day1) was started as the fourth-line treatment. He developed a fever of 39.0°C or less on day 11, and his neck and legs gradually became sore. He was transported by ambulance to our hospital because of depressed consciousness on day 16. On fluid-attenuated inversion recovery (FLAIR) MRI

Table 1. Summary of Three Cases With Aseptic Meningitis Induced by Atezolizumab

Case	Age	Sex	Histologic Type	PD-L1 Expression	Treatment	Symptoms of Meningitis	Time of Onset of Meningitis From the Start of Atezolizumab	Cerebrospinal Fluid Findings	Cytology	Treatment for Meningitis	Clinical Outcome of Meningitis
1	71	F	Not otherwise specified	Unknown	CBDCA + PTX + BEV + Atezolizumab (first line)	Fever and disturbance of consciousness	14 d	Cell→, Protein↑	Class II	Steroid pulse (1000 mg × 3 d)	Improved
2	55	M	Adenocarcinoma	1%-24%	Atezolizumab (second line)	Fever and disturbance of consciousness	11 d	Cell→, Protein↑	Class I	Steroid pulse (1000 mg × 3 d)	Improved
3	50	M	Adenocarcinoma	1%-24%	Atezolizumab (fourth line)	Fever and disturbance of consciousness	11 d	Cell↑, Protein↑↑	Class II	Steroid pulse (1000 mg × 3 d)	Improved

PD-L1, programmed death-ligand 1; CBDCA, carboplatin; PTX, paclitaxel; BEV, bevacizumab; F, female; M, male.

Figure 1. Findings of fluid-attenuated inversion recovery magnetic resonance imaging after angiography in case 3 immediately after onset of depressed consciousness (*A*) and 4 days after the administration of methylprednisolone (*B*). Abnormal enhancements were found along the lines of the corpus callosum in Figure 1*A* (yellow arrows), which disappeared in Figure 1*B*.

after angiography, multiple abnormal enhancements were found along the lines of the corpus callosum (Fig. 1*A*). There was an increased number of cells, mainly composed of monocytes (15/μL), and an increased level of protein (358 mg/dL) in the CSF. The sugar level in the CSF was 57 mg/dL, which was within the reference range. Smears of acid-fast bacteria and other common bacteria were negative. As the cytology of the CSF was class II, drug-induced meningitis owing to atezolizumab use was suspected. Atezolizumab was discontinued, and methylprednisolone (1000 mg for 3 d), combined with an antiepileptic drug (levetiracetam), was started on day 42. MRI taken 4 days after administration of methylprednisolone revealed disappearance of the abnormal enhancements (Fig. 1*B* and Table 1).

Discussion

Encephalitis and meningitis are reported to occur more frequently with atezolizumab than with other ICIs, and Japanese patients are said to be predisposed to these irAEs. Of the 25 patients who were treated with atezolizumab in our department, three (12%) developed meningitis. This incidence rate is higher than that reported in the OAK study, which included not only Japanese patients but also those from other countries.[4,7]

Among the Japanese patients registered in OAK study, encephalitis and meningitis occurred on days 14 to 16 of cycle 1, which was very similar to the time of onset in the present study. In CSF examination, the number of cells and the protein level were normal to slightly high and high, respectively, which differed from the findings typically observed in cases of infectious meningitis. Furthermore, given the lack of malignant findings on the CSF cytologic examination, carcinomatous meningitis was ruled out, and we ultimately diagnosed the patients with atezolizumab-induced meningitis. When patients develop neurologic symptoms while undergoing treatment with ICIs, specifically atezolizumab, CSF examinations should be routinely performed to differentiate between infectious meningitis and carcinomatous meningitis.

In a report regarding encephalitis and meningitis caused by cytotoxic T-lymphocyte–associated protein 4 inhibitors, a high signal intensity on meninges was mentioned in some cases.[8] One of the three cases in our study exhibited abnormal enhancement along the lines of the corpus callosum on FLAIR MRI after angiography. This finding is assumed to have been induced by immune-related meningitis owing to atezolizumab use as the finding disappeared after administration of methylprednisolone.

To our knowledge, there have been no detailed reports of encephalitis and meningitis mediated by atezolizumab in patients with NSCLC, making the current report the first to describe detailed information on atezolizumab-induced aseptic meningitis. We believe that the findings obtained in our three cases include several informative lessons. First, atezolizumab-induced meningitis develops from approximately day 15 after the first administration of atezolizumab; second, fever may be the first symptom of atezolizumab-induced meningitis; and third, a slight increase in cells and a marked increase in the protein level can be observed in the CSF. These findings can be the basis of a diagnosis of meningitis mediated by ICIs. In addition, despite the lack of abnormal findings on T1- and T2-weighted MRI, such findings can be seen on FLAIR imaging after angiography. Regarding the treatment of immune-related meningitis, steroid pulse therapy resulted in prompt improvement of the consciousness level in all three cases.

In summary, a variety of irAEs have been reported, some of which are difficult to control. Among them, immune-related encephalitis and meningitis often lead to severe symptoms and a dismal prognosis, and so they should be treated as promptly as possible. We believe that the current report offers thoracic oncologists important information in the diagnosis, treatment, and clinical course of atezolizumab-induced meningitis.

Acknowledgments

The authors thank Brian T. Quinn for his critical comments on the manuscript.

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