CASE REPORT

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Lorlatinib-Related Vision Loss: Two Cases of Non-Small Cell Lung Cancer with Blindness

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ABSTRACT Data on the management of Grade 3-4 visual disorders due to lorlatinib remain limited. We presented two cases of Grade-4 vision loss due to lorlatinib. We interrupted lorlatinib and initiated a pulse steroid in these patients. In our first patient, visual function improvement was observed three days after treatment, with complete visual function recovery at the end of the first month. However, in the second patient, although vision loss returned to the extent of limited vision from 3 m, no further improvement was noted. In both patients, lorlatinib was continued at a reduced dose because of a favorable response and visual function improvement. In conclusion, the early recognition of vision loss and the interruption of lorlatinib may be effective in the successful recovery of visual function loss. Concurrent steroid therapy may also be beneficial.

Keywords: Blindness; lorlatinib; vision disorders

Lorlatinib is a third-generation inhibitor of anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1) and is used in non-small cell lung cancer (NSCLC) therapy.[1] The CROWN study evaluated lorlatinib versus crizotinib in the first-line treatment of patients with NSCLC. The most common side effects reported in the study were lipid profile disorders and edema, and visual disturbances were observed in 18% of the patients. No Grade 3-4 toxicity was observed.[2] Data on the management of Grade 3-4 visual disorders due to lorlatinib remain limited. Cases of blindness have been reported with crizotinib, a first-generation ALK inhibitor.[3] We presented two cases of Grade-4 vision loss due to lorlatinib.

CASE REPORTS

CASE 1

A 55-year-old male patient presented with hemoptysis and was provided a diagnosis of Stage 3B lung adenocarcinoma. The patient received concurrent radiotherapy with a platinum doublet regimen, followed by consolidation chemotherapy. He presented with shortness of breath and bone pain three months after treatment completion. Imaging revealed metastases in both lungs, mediastinum, liver, and bones. ALK gene rearrangement was detected in molecular analysis. Alectinib was initiated as first-line therapy, which elicited the partial response (PR) as the best response. The lesion in the right lung and mediastinal lymph nodes progressed 18 months after treatment. Lorlatinib 100 mg/day was initiated as the second-line treatment. The patient, without any vision problems before treatment, developed vision loss two months after treatment, with difficulty seeing a distance of 1 m. Positron emission tomography-computed tomography was performed to evaluate NSCLC control, with the results indicating a satisfactory PR. Brain magnetic resonance imaging (MRI) revealed normal findings. Because an eye examina-

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tion revealed optic neuropathy, lorlatinib was interrupted, and a pulse steroid was initiated. The steroid dose was slowly reduced, and the treatment was completed in 1 month. Visual function improvement was observed three days after treatment, with the recovery of full vision detected at the end of the first month. Subsequently, lorlatinib was reinitiated at a lower dose. The treatment is being continued without any additional side effects. An informed consent form was obtained from the patient.

CASE 2

A 55-year-old male patient presented with a cough and shortness of breath. Imaging studies revealed a massive mass in the right lung, metastatic nodules in the contralateral lung, and diffuse metastases in the liver and bones. Lung biopsy revealed adenocarcinoma, and ROS1 positivity was detected in molecular analysis. Crizotinib was initiated as the first-line treatment. Eye examinations were normal before and during crizotinib treatment. Disease progression with new metastases in the cerebellar hemisphere, contralateral lung, liver, and skeletal system was observed 15 months after treatment. Stereotactic radiation therapy (SRT) was administered for brain metastasis, followed by lorlatinib 100 mg/day as the second-line treatment. The patient had mild visual hallucinations on the 15th day of treatment, with the symptoms resolving after dose modification. Because of nearly complete vision loss three months after treatment, the patient presented to an external center. Optic neuropathy was detected on examination. Follow-up imaging was performed in our polyclinic on the 23rd day of vision loss. An eye examination revealed optic atrophy. Lorlatinib was interrupted, and a pulse steroid was administered. The evaluation of disease control was concluded as satisfactory PR on the basis of positron emission tomography-computed tomography findings. No intracranial pathology was detected using the brain MRI. Steroid therapy was reduced and discontinued within 4-6 weeks. Although the vision loss returned to limited vision from 3 m, no further improvement was noted. Lorlatinib was continued at a reduced dose because of the satisfactory response and stability in vision loss. An informed consent form was obtained from the patient.

DISCUSSION

We herein presented two cases of vision loss due to severe ocular toxicity that occurred during lorlatinib use. Although the etiology of vision loss is multifactorial, we believe lorlatinib to be the most likely cause in these cases. The conclusion was based on the sequence of events and the absence of findings in intracranial imaging that may cause vision loss. Moreover, optic nerve tumor involvement is an unlikely cause of bilateral vision loss because of the absence of mass development in repeat MRIs for both patients. Intracranial metastasis in one of our patients was not in an area that would affect vision; moreover, the metastasis regressed with SRT, followed by lorlatinib.

Visual toxicities associated with the first-generation ALK inhibitor crizotinib have been reported more frequently in the literature.[4] Chun et al. presented the case of a 69-year-old female patient who developed crizotinib-related vision loss.[3] In this case, after treatment initiation, crizotinib was restarted due to favorable tumor response, and vision stabilization was achieved.[3] Visual disturbances due to ALK inhibitors are rare but include trailing lights and palinopsia, especially during transitions from dark to light.[5] Visual disturbances related to lorlatinib have been reported in clinical studies; however, such adverse effects are fewer than those related to crizotinib and are mostly Grade 1-2 toxicities.[2,4]

Data on lorlatinib-related visual loss are limited. In the first patient, we achieved complete recovery in vision loss by interrupting lorlatinib and initiating steroids. However, although the same treatment was administered to our second patient, complete visual function recovery was not achieved. Because of the delay in the admission of the second patient to our clinic, we could not interrupt lorlatinib and initiate steroids in the early period, which may have played a role in incomplete visual function recovery. Therefore, the application of appropriate treatment is crucial in the management of serious adverse effects, such as vision loss. We could not confirm whether the cause of vision loss improvement was steroid administration or drug discontinuation. Therefore, data from more patients are required to validate these re-

sults. In addition, the absence of visual field examination reports in these two cases is a limitation.

In conclusion, the early recognition of vision loss and the interruption of lorlatinib may be effective in the successful management of visual function loss. Concurrent steroid therapy may also be beneficial.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Serdar Karakaya;* ***Design:*** *Serdar Karakaya;* ***Control/Supervision:*** *İbrahim Karadağ, Şebnem Yücel;* ***Data Collection and/or Processing:*** *Şeyma Işık;* ***Analysis and/or Interpretation:*** *Serdar Karakaya;* ***Literature Review:*** *Serdar Karakaya, Özgen Ahmet Yıldırım;* ***Writing the Article:*** *Serdar Karakaya, Şeyma Işık;* ***Critical Review:*** *Özgen Ahmet Yıldırım;* ***References and Fundings:*** *Serdar Karakaya;* ***Materials:*** *Serdar Karakaya.*

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