

Pancytopenia During Osimertinib Treatment in a Patient with EGFR-Mutated Non-Small Cell Lung Cancer

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Background: Osimertinib is an irreversible tyrosine kinase inhibitor approved for the treatment of metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). In clinical trials, osimertinib has exhibited excellent activity and less toxicity compared to gefitinib, erlotinib and standard chemotherapy.

Case Presentation: Herein, we describe the case of a 69-year-old man who received first-line osimertinib for metastatic EGFR-mutated NSCLC. Suspected osimertinib-induced pancytopenia together with a partial treatment response was assessed after 10 days of therapy. Osimertinib was resumed at 40 mg daily a month later while the patient exhibited durable stable disease. No other adverse events occurred.

Conclusion: In the current case, first-line treatment with osimertinib at 80 mg daily in a patient with EGFR-mutated NSCLC resulted in severe pancytopenia and a rapid treatment response. Dose reduction to 40 mg daily resulted in excellent activity without any further adverse events. Osimertinib could be safely resumed at a reduced dose even after pancytopenia.

Keywords: adverse events, anemia, EGFR, neutropenia, non-small cell lung cancer, osimertinib, pancytopenia, thrombocytopenia

Introduction

Approximately 15–20% of metastatic non-small cell lung cancer (NSCLC) is associated with clinically relevant epidermal growth factor receptor (EGFR) mutations (L858R mutation in exon 21 and deletions in exon 19).¹ Osimertinib is an oral third-generation irreversible tyrosine kinase inhibitor of EGFR and was the first drug shown to be superior to second-line platinum-pemetrexed chemotherapy in patients with metastatic EGFR-mutated T790M-positive NSCLC.^{2,3} In clinical trials in patients with untreated metastatic EGFR-mutated NSCLC those treated with osimertinib exhibited better progression-free survival and overall survival than those treated with gefitinib and erlotinib.⁴

Metastatic disease in the central nervous system (CNS) is common in patients with metastatic NSCLC and is associated with lower overall survival. First- and second-generation EGFR tyrosine kinase inhibitors (TKIs) exhibited suboptimal activity in the CNS due to limited capacity to cross the blood-brain barrier.⁵ In preclinical and clinical studies, osimertinib was broadly distributed in the brain, with greater exposure than gefitinib and erlotinib.⁵ The most common adverse events associated with osimertinib are diarrhea, rash, dry skin, paronychia, reduced appetite, stomatitis, fatigue, nausea and hematologic abnormalities.^{3,4,6,7} Grade 3–5 serious neutropenia, anemia and thrombocytopenia occur in <2% of patients during treatment with osimertinib.^{3,4,6,7}

Herein we describe the case of a patient who exhibited a rapid treatment response and severe pancytopenia after 10 days of osimertinib at the full dose. The case has important clinical implications because it is the first time that

osimertinib was not completely discontinued, but was instead resumed at a reduced dose after rapid recovery of laboratory parameters and clinical condition.

Case Report

A 69-year-old man who had never smoked was admitted to the hospital for chest pain and dyspnea in October 2019. He had no significant medical history. He was not taking any medication. Whole-body computed tomography and brain magnetic resonance imaging revealed a 3.5 x 5.0-cm pulmonary mass in the upper left lobe, mediastinal lymphadenopathies and multiple brain metastases, the largest of which was approximately 1 cm along its longest axis in the left temporal lobe. Stage IVB (T3N2M1c) lung adenocarcinoma was diagnosed by biopsy performed via bronchoscopy. Biopsied tumor tissue revealed the presence of EGFR exon 19 deletion, no ALK translocations, no ROS1 translocations and PD-L1 expression of 20% determined via the SP263 PDL-1 assay.

Osimertinib was administered at the standard dose of 80 mg daily from November 2019. Brain radiotherapy was not performed given osimertinib activity in the CNS. The patient exhibited grade 4 neutropenia (4×10^6 cells/L), grade 3 anemia (7.8 g/dL) and grade 2 thrombocytopenia (62×10^9 cells/L) 10 days after starting osimertinib. Reticulocytes were undetectable. Serum biochemical indices of liver and kidney function were normal. Hematological iron, folate and B12 deficiencies were excluded. Hemolytic anemia screening was negative. Bacterial and fungal infections were excluded based on negative blood cultures. Osimertinib was discontinued. Two-unit red blood cell transfusions were performed immediately in conjunction with administration of granulocyte colony-stimulating factors (subcutaneous filgrastim 480 cg daily for 3 days). The patient was refractory to granulocyte colony-stimulating factors and grade 3 neutropenia (6×10^6 cells/L) and grade 3 thrombocytopenia (45×10^9 cells/L) were still evident 3 days after the onset of bone marrow toxicity. Bone marrow cellularity and trilineage progenitor cells were not investigated because the patient did not consent to bone marrow aspiration and biopsy. After 10 days of supportive care with blood transfusions (four units in total) and 5 days of granulocyte colony-stimulating factor daily (subcutaneous filgrastim 480 cg) however, normal blood parameters were detected (hemoglobin 13.2 g/dL, neutrophil count 40×10^6 cells/L, platelet count 155×10^9 cells/L). Tests for rheumatic factors, ANA, c-ANCA, p-ANCA, *Brucella*, cytomegalovirus virus, parvovirus, Epstein–Barr virus, HIV, hepatitis B virus and hepatitis C virus were negative. The patient's karyotype was normal. In the absence of other causes, osimertinib-induced pancytopenia was suspected. In December 2019 computed tomography indicated a partial tumor response with reduction of brain and thoracic malignant lesions. Specifically, the diameters of the pulmonary mass in the upper left lobe had decreased from 3.5x5.0 cm to 2.1x2.0 cm, mediastinal lymphadenopathies had decreased in size and number and the largest brain metastasis had shrunk from 1.0 cm to 0.5 cm on its longest axis. The Eastern Cooperative Oncology Group Performance Status of the patient was 0. Given the potential clinical benefit, in January 2020 osimertinib was resumed at a reduced dose of 40 mg daily in conjunction with weekly laboratory monitoring. In March 2020 computed tomography indicated stable disease. No adverse events occurred after the osimertinib dose reduction. To date, the patient remains on 40 mg osimertinib and is exhibiting stable disease.

Discussion

The mechanisms underlying toxicity related to EGFR inhibitors are still unknown. Osimertinib is an irreversible EGFR TKI.² In the AURA3 clinical trial osimertinib was associated with better progression-free survival and less toxicity compared to standard chemotherapy in patients with metastatic T790M-positive NSCLC previously treated with an EGFR TKI.^{3,4} In the FLAURA clinical trial, osimertinib performed better than gefitinib and erlotinib in patients with untreated metastatic EGFR NSCLCs and was associated with a better safety profile.⁵ Severe anemia, thrombocytopenia and neutropenia were extremely rare.^{3–7}

In a retrospective study, Kishikawa et al reported only one case of grade 3 neutropenia in a patient with T790M-positive NSCLC treated with osimertinib after disease progression to another EGFR TKI.⁸ Yi et al reported that osimertinib was well tolerated by most patients and common adverse events included diarrhea, rash, dry skin, paronychia, reduced appetite, stomatitis, fatigue, nausea, pruritus and dyspnea.⁷ Mezquita et al reported greater activity associated with osimertinib compared to chemotherapy in patients with pretreated T790M-positive EGFR-mutated

NSCLC and better progression-free survival compared to gefitinib and erlotinib, with a similar toxicity profile but fewer serious adverse events. Hematological abnormalities were rare.⁹

The most frequently described hematological adverse event is neutropenia.⁷ Two cases of osimertinib-induced pancytopenia and aplastic anemia in patients with T790M-positive EGFR-mutated NSCLC have been reported. A 78-year-old Japanese woman with a metastatic NSCLC was administered first-line gefitinib for 14 months and second-line chemotherapy for 2 months. Chemotherapy was followed by treatment with osimertinib after detection of T790M mutation. Pancytopenia occurred after 31 months of therapy and severe hypocellular bone marrow with few myeloid and erythroid cells at any stage of differentiation as well as hardly any identifiable primitive progenitor stem cells was described. Osimertinib was permanently discontinued and the patient underwent immunosuppressive therapy with red blood cell and platelet transfusions as required. Stable disease was documented for 12 months after osimertinib discontinuation.¹⁰

Kim et al described the case of a patient with metastatic NSCLC who received platinum-based chemotherapy and gefitinib before osimertinib.¹¹ After 19 weeks of osimertinib, the patient developed pancytopenia with severe thrombocytopenia, anemia and agranulocytosis. Bone marrow biopsy revealed severe aplastic anemia. The patient died from a spontaneous intracranial hemorrhage. To the best of our knowledge, the only case of pancytopenia secondary to aplastic anemia induced by first-line osimertinib in a patient with metastatic EGFR-mutated NSCLC was described by Sala et al.¹² That patient developed severe aplastic anemia after 21 weeks of osimertinib. Palliative bone radiotherapy was performed in the right femur, right iliac wing and cervical-dorsal spinal cord during osimertinib administration. Despite several antibiotic treatments, the patient died after 7 weeks of neutropenia. In these three cases, pancytopenia with aplastic anemia induced by osimertinib occurred after chemotherapy or palliative radiotherapy.

The pathogenesis of osimertinib-induced aplastic anemia is unknown. Acquired aplastic anemia has been causally associated with several drugs and conditions. The three major causes of acquired aplastic anemia are metabolite-driven toxicity, immune-related mechanisms and direct toxicity.^{13,14} In the current case suspected aplastic anemia with pancytopenia developed during treatment with osimertinib in the absence of other causes such as concomitant medications, previous chemotherapy, bone palliative radiotherapy, infection and autoimmune disease. Serum creatinine was not increased.¹⁵

This is the first report of pancytopenia without other concomitant causes such as previous chemotherapy, bone palliative radiotherapy, concomitant medication or concomitant autoimmune disease. Notably however, the lack of a diagnostic bone biopsy due to a lack of patient consent may be the most important limitation of the present case report. To our knowledge, this is the first report of a rapid tumor response after 10 days of treatment with osimertinib complicated by a rare toxicity. In contrast with other previously reported cases, osimertinib was not permanently discontinued and was instead resumed at a lower dose after the rapid recovery of clinical condition and laboratory parameters. A treatment switch from osimertinib to first- or second-generation EGFR TKIs was excluded because of the patient's rapid response after a few days of osimertinib and lower activity in the CNS of first- and second-generation EGFR TKIs in patients not previously treated with brain radiotherapy.⁵ The pathophysiological basis of the pancytopenia and suspected reversible aplastic anemia in the current patient are unknown.

To our knowledge, this is the first report of a case of pancytopenia with suspected osimertinib-induced aplastic anemia that was fully reversed after treatment discontinuation. For the first time osimertinib was resumed at a lower dose and thereafter exhibited an excellent safety profile while maintaining good activity. Vigilant laboratory monitoring should be undertaken during treatment with osimertinib, greater attention should be directed to rare potential adverse events, given emerging indications for osimertinib in patients with non-metastatic EGFR-mutated NSCLC.¹⁶ A dose reduction to 40 mg osimertinib daily resulted in sustained activity and good tolerability in a patient with metastatic NSCLC.

Conclusion

Herein we have described a case of osimertinib-related pancytopenia in conjunction with a rapid tumor response. After osimertinib discontinuation and recovery from hematological toxicity osimertinib was resumed at a lower daily dose of 40 mg, resulting in excellent activity and no subsequent adverse events. Osimertinib can be safely resumed with a dose reduction, even following pancytopenia.

Consent Statements

The patient has provided written informed consent for the details of their case to be published. Institutional approval from the Oncology Unit of SS Annunziata Hospital, Chieti, Italy, was obtained to publish the report.

Acknowledgments

This work was supported by the Consorzio Interuniversitario Nazionale per la Bio Oncologia.

Disclosure

The authors report no conflicts of interest pertaining to this work.

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