

Rapid Development of Infusion-Related Severe Hypotension During Rituximab Therapy

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Rituximab, a chimeric anti-CD20 monoclonal antibody targeting B cells, is well demonstrated to have high response rates in chronic lymphocytic leukemia (CLL).^{1,2} It has several mechanisms of action including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, induction of apoptosis, and sensitization to chemotherapy.³

Infusion-related adverse events are common in many patients during the first infusion of rituximab.² Rituximab-associated adverse events have been reported to occur 30 minutes to 2 hours after the start of the infusion and are thought to be due to cytokine release. These adverse events include flushing, rigors or chills, maculopapular erythematous skin rash, urticaria, and pruritus. More severe reactions, such as tachycardia, bronchospasm, hypotension, and death, have also been documented.^{2,4}

We describe an elderly male patient with CLL, previously unexposed to rituximab therapy, who experienced severe hypotension 5 minutes after the start of the first rituximab infusion.

Case Report

An 84-year-old white male with coronary artery disease and Rai stage IV CLL that included lymphocytosis, anemia, and thrombocytopenia presented to the emergency department with chest pain. Physical examination showed

OBJECTIVE: To report an incident of rapid development of profound hypotension, differing from the time described in previous reports, during the infusion of rituximab chemotherapy in a patient without prior exposure to the drug.

CASE SUMMARY: An 84-year-old white male with Rai stage IV chronic lymphocytic leukemia was prescribed rituximab 375 mg/m² by intravenous infusion. Rituximab 50 mg/h was initiated after premedication with acetaminophen, diphenhydramine, dexamethasone, and ondansetron 3 days into his hospital course. Five minutes after the infusion had begun, he experienced a significant decrease in blood pressure to 76/45 mm Hg, and the infusion was stopped. After 30 minutes, the blood pressure returned to normal. Rechallenge with rituximab 25 mg/h was attempted, but the blood pressure again declined and the patient experienced chills and rigors. The infusion was discontinued, and the symptoms resolved 1 hour later.

DISCUSSION: Infusion-related adverse reactions associated with rituximab are reported at a higher rate than with other monoclonal antibodies. Hypotension with rituximab has been reported to occur 30 minutes to 2 hours after initiation of the infusion. In contrast, severe hypotension in our patient occurred within 5 minutes after the infusion was started in a patient with no previous exposure to the drug. While many studies hypothesize that cytokine release from lymphocytes and tumor cell agglutination might contribute to severe infusion-related reactions with rituximab, the mechanism of action is not yet known. Use of the Naranjo probability scale indicated that the hypotension was probably associated with rituximab administration.

CONCLUSIONS: Awareness of the rapidity of this adverse effect in patients who have not received prior treatment with monoclonal antibodies is important during chemotherapy treatment.

KEY WORDS: adverse drug reaction, hypotension, infusion-related toxicity, rituximab.

Ann Pharmacother 2011;45:xxxx.

Published Online, 19 Apr 2011, *theannals.com*, DOI 10.1345/aph.1P733

normal temperature, pulse 115 beats/min, respirations 22 breaths/min, blood pressure 137/85 mm Hg, oxygen saturation 85%, and 2+ edema at the ankle. The body surface area was calculated to be 1.82 m² based on his height of 170 cm and weight of 73.6 kg. He was alert without significant distress upon examination, and reported pain of 7 on a 10-point scale. Complete blood cell count with differential revealed white blood cells 107,000 cells/ μ L, hemoglo-

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bin 11.8 g/dL, platelets 195,000 cells/ μ L, and lymphocytes 91%. Electrocardiography examination showed sinus tachycardia at a rate of 114 beats/min. Chest X-ray showed mild cardiomegaly with pulmonary vascular congestion. There was no history of exposure to rituximab and no drug allergies were reported. Hospital-prescribed medications included metoprolol, amlodipine, atorvastatin, irbesartan, clopidogrel, and multivitamins. After relief of the chest pain, the patient was admitted and received a port placement for administration of chemotherapy.

Twelve hours before the initiation of rituximab chemotherapy, the physician discontinued amlodipine and metoprolol. On hospital day 3, 1 hour prior to rituximab chemotherapy, the patient's vital signs were temperature 36.7 °C, pulse 74 beats/min, respirations 20 breaths/min, oxygen saturation 97%, and blood pressure 132/71 mm Hg. He was stable, alert, and oriented. One hour preceding rituximab chemotherapy, the patient received oral acetaminophen 650 mg, intravenous diphenhydramine 50 mg, ondansetron 14 mg, and dexamethasone 10 mg. Rituximab, at a dose of 375 mg/m² by intravenous infusion, was initiated at a rate of 50 mg/h. Five minutes after the infusion began, the patient experienced a substantial decrease in blood pressure to 76/45 mm Hg. Following an additional 5 minutes (10 minutes after infusion start time), his blood pressure declined further to 72/44 mm Hg; he remained alert and oriented. The physician instructed that the infusion be discontinued. The patient was given intravenous normal saline and methylprednisolone 80 mg.

Vital signs were measured 30 minutes after the infusion was discontinued; blood pressure was stabilized at 117/73 mm Hg. Rituximab was administered as a rechallenge at a rate of 25 mg/h, half the rate of the initial infusion. Despite additional supportive therapy with intravenous meperidine 25 mg, the patient experienced rigors and extreme chills, with shaking during the infusion. His blood pressure was 96/52 mm Hg 20 minutes after the second infusion began. Although oxygen saturation declined from 99% to 80%, his pulse and respirations remained steady at 78 beats/min and 18 breaths/min, respectively. The physician discontinued rituximab. The patient's blood pressure recovered to 132/71 mm Hg and oxygen saturation was 90% 1 hour after the rituximab infusion was discontinued. Despite the physiological stabilization and supportive medications, the patient's rigors and chills did not resolve until the following day.

Discussion

In clinical trials, rituximab demonstrated efficacy in previously untreated patients with stage III or IV B-cell CLL, as well as those with relapsed or refractory disease.² Studies have shown that the frequency of initial infusion reactions with rituximab is higher, at 77%, than with

trastuzumab (40%), cetuximab (12-19%), or panitumumab (4%).^{2,5-7} Death has also been reported, with an incidence of approximately 0.04-0.07%, especially in patients who have not received prior chemotherapy.^{2,5} The incidence and severity of adverse reactions such as shaking, rigors, hypotension, or other infusion-related symptoms can be lessened by premedication with acetaminophen, corticosteroids, and histamine H₁-blockers. However, there is still more than a 10% frequency of grade III-IV infusion reactions.¹

Rituximab prescribing information and clinical trials have documented that adverse reactions such as hypotension occur 30 minutes to 2 hours after the infusion is started.^{2,5,7} However, in contrast to that information, our patient experienced a significant decrease in blood pressure within 5 minutes after the infusion began. A literature search and consultation with a clinical information representative of the manufacturer of rituximab (Genentech; South San Francisco, CA) did not reveal any reports (internal or published) related to infusion reactions, particularly hypotension, associated with rituximab or any other monoclonal antibodies occurring that quickly.

Studies have yet to explain the reasons and pathway of infusion-related hypotension. Researchers have suggested that cytokine release from lymphocytes might be responsible for this adverse reaction.⁶⁻⁸ The mechanism of infusion reaction symptoms of fever, chills, dyspnea, and hypotension are proposed to be secondary to increases in serum tumor necrosis factor- α and interleukin-6 after 90 minutes of rituximab infusion.⁷

However, the incidence of infusion-related adverse drug events can be reduced. The rituximab prescribing information recommends premedicating the patient 1 hour prior to starting the infusion with acetaminophen, diphenhydramine, and corticosteroids.⁹ If patients receiving monoclonal antibodies experience these adverse drug events, restarting the infusion at half of the initial infusion rate may resolve the reactions.⁹ However, reports have indicated that modifying the infusion time may not alleviate reactions from monoclonal antibodies. Breslin reported on a patient who did not tolerate rechallenge at 50% of the initial infusion (25 mg/h), with a continual decline in blood pressure despite appropriate administration of premedications.¹⁰ The patient also reported adverse reactions such as pain and chills, regardless of meperidine and other supportive care.¹⁰

In our report, use of the Naranjo adverse drug reaction probability scale indicated a probable relationship between the rituximab chemotherapy and the development of severe hypotension.¹¹ Furthermore, the resolution of the symptoms soon after discontinuation of rituximab supports the suggestion of its involvement in the rapid development of severe hypotension.

This is a unique episode of a rituximab-related adverse reaction due to the rapidity of the onset of hypotension during the initial infusion in a patient with no exposure to the drug. We believe that this abrupt decline in blood pressure was associated with rituximab. Considering the possibility of such a rapid decrease in blood pressure, clinicians should take precautions to monitor for this adverse effect in patients receiving rituximab immediately after beginning the infusion.

To our knowledge, the rapid infusion-related reaction of severe hypotension associated with rituximab in our patient is unique. Previous reports, including the prescribing information, have not indicated similar reactions occurring less than 30 minutes after the initiation of the infusion. This case report is not only unique in the rapidity in which the adverse event occurred, but also that the patient had previously not received any treatment with monoclonal antibodies. Awareness of this adverse effect is important when administering a chemotherapy regimen that includes rituximab.

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Reprints/Online Access: www.theannals.com/cgi/reprint/aph1.P733

Conflict of interest: Authors reported none

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