CASE REPORT

Necrotising fasciitis after bortezomib and dexamethasone-containing regimen in an elderly patient of Waldenström macroglobulinaemia

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SUMMARY

Bortezomib and high-dose dexamethasone-containing regimens are considered to be generally tolerable with few severe bacterial infections in patients with B-cell malignancies. However, information is limited concerning the safety of the regimen in elderly patients. We report a case of a 76-year-old man with Waldenström macroglobulinaemia who suffered necrotising fasciitis without neutropenia after the combination treatment with bortezomib, high-dose dexamethasone and rituximab. Despite immediate intravenous antimicrobial therapy, he succumbed 23 h after the onset. Physicians should recognise the possibility of fatal bacterial infections related to bortezomib plus high-dose dexamethasone in elderly patients, and we believe this case warrants further investigation.

BACKGROUND

The development of molecular targeting agents has led to a paradigm shift in the treatment of B-cell malignancies. Bortezomib was initially approved by the US Food and Drug Administration (FDA) in 2003 for the treatment of multiple myeloma (MM) as the first proteasome inhibitor agent.¹

Bortezomib is frequently combined with high-dose dexamethasone or prednisone, which has a high activity for MM.^{2,3} Recent small-sized studies have shown that combination chemotherapy comprising bortezomib, dexamethasone and rituximab (BDR) is promising with no severe bacterial infections for Waldenström macroglobulinaemia (WM) and mantle cell lymphoma.^{4,5} However, most patients enrolled into these studies were younger than the general patient population, and without comorbidities, and the safety and effectiveness of the BDR regimen are not fully investigated in elderly patients or those with some complications. We report a case of an elderly man with WM who developed fatal necrotising fasciitis (NF) after the BDR chemotherapy.

CASE PRESENTATION

A 76-year-old man was transferred to our hospital due to appetite loss and fatigue. The elevated serum levels of IgM (1944 mg/dL) and examination of bone marrow biopsy confirmed the diagnosis of WM. His performance status on admission was one, defined by the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.⁶ His blood test showed anaemia (haemoglobin 9 g/dL) and elevated serum β 2-microglobulin level (3.4 mg/L).

Owing to general fatigue, anaemia and renal impairment, we initiated the BDR chemotherapy for rapid disease control, which consisted of bortezomib 1 mg/m² subcutaneously; dexamethasone 40 mg/body intravenously on days 1, 4, 8, 19, 31 and 34 and rituximab 375 mg/m² intravenously on day 19.⁷ He responded to the regimen, and a serum level of IgM was decreased to 933 mg/dL on day 31. The nadir of white cell counts (WCCs) and neutrophil counts was 3.0×10^9 and 2.2×10^9 /L, respectively. He developed mild diarrhoea (grade 1) on day 31. We did not use antibiotics at that time because we diagnosed that diarrhoea was the adverse reaction of bortezomib.

On day 36, the patient developed a high-grade fever (38.7°C). His blood pressure was decreased to 91/32 mm Hg, and heart rate was 98 bpm.

INVESTIGATIONS

Physical examination showed severe pain and swelling of his right thigh without wounds. WCCs were 15.0×10^9 /L with 88% neutrophils. Two sets of blood cultures were taken and the fascia biopsy was excised from the right thigh by an orthopaedist at his bedside. It revealed neutrophilic infiltration and multiple Gram-negative rods, morphologically consistent with Enterobacteriaceae.

DIFFERENTIAL DIAGNOSIS

With fever, decreased blood pressure, increased heart rates and elevated WCCs, he was clinically diagnosed with septic shock. Among the soft tissue infections, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score might be a useful diagnostic tool for a differential diagnosis.⁸ Although the LRINEC score was 5 (positive value: 6 or more) in our patient, we suspected NF based on his clinical course with his severe pain, swelling, systemic toxicity and acute onset. The findings of the biopsy proved the diagnosis of NF.

TREATMENT

We initiated intravenous administration of meropenem (1 g) and vancomycin (1 g) when he was clinically diagnosed with septic shock. We also performed the open incisions to the necrotic lesions for drainage.

OUTCOME AND FOLLOW-UP

After the diagnosis of NF, he was moved to the intensive care unit. Despite the necrotic lesion drainage and administration of the antibiotics, he

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died of rapid disease progression 23 h after the onset. *Klebsiella pneumoniae* was cultured from the specimens of blood, tissue and tissue fluids. Autopsy showed erosive inflammations from the small bowel to the ascending colon.

DISCUSSION

We report a case of fatal bacterial infection in an elderly patient with WM. It should be noted that his general condition prior to the chemotherapy was good, and that he had never developed neutropenia during chemotherapy. Furthermore, he had no risk factors of NF including trauma, decubitus ulcer, diabetes or liver cirrhosis. These findings suggest the possible association between the fatal bacterial infection and the BDR chemotherapy.

Since *K pneumoniae* is a common indigenous microflora of the gut, we assume that it might translocate through the gut into the systemic circulation. Interestingly, he developed mild diarrhoea on day 31, and erosive lesions of the gut were confirmed by autopsy. The bowel lesions probably played a role as a portal of entry for the fatal bacteraemia.

Systemic evaluation prior to the chemotherapy failed to show any abnormal findings in the gastrointestinal tract. It is noteworthy that gastrointestinal manifestations are one of the common adverse effects of bortezomib. According to a phase III trial on bortezomib for MM, 57% (190/331) of patients developed diarrhoea of all grades, and 7% (24/331) developed diarrhoea of grade 3.⁹ These findings suggest the association between the bowel lesions and bortezomib in our patient.

The contribution of rituximab in developing NF was unlikely. The patient received only one dose of rituximab on day 19. Moreover, a systematic review revealed that the addition of rituximab to chemotherapy did not increase the global risk of infections; nor did it increase the risk of lethal infections in patients with malignant lymphomas.¹⁰

In addition to bortezomib, high-dose dexamethasone probably played an important role in the pathogenesis of fatal bacteraemia. High-dose dexamethasone increases the risk of infections in immunocompromised patients, especially in elderly patients. High-dose dexamethasone in combination with lenalidomide was associated with high mortality in patients with MM older than 65 years.¹¹ There is also a case report, in which a 65-year-old patient with MM developed *Salmonella enteritidis* NF after bortezomib and dexamethasone.¹² In previous studies, patients younger than 65 years have often been exclusively enrolled for MM using bortezomib and high-dose dexamethasone.^{13 14} However, the median age at diagnosis for MM is 69 years.¹⁵ A lower dose of dexamethasone may improve prognosis with lower toxicity for elderly patients with MM⁹ as well as WM.

In conclusion, the safety of bortezomib and dexamethasone-containing regimens is not sufficiently validated for elderly patients, who constitute the majority of the population of haematological malignancies, and awaits further investigation.

Learning points

- Gastrointestinal adverse reactions of bortezomib may lead to enterobacterial infections.
- The more appropriate dose of dexamethasone for elderly patients of B-cell malignancies awaits further investigation.
- Necrotising fasciitis should be ruled out in haematological patients with severe pain, swelling and systemic toxicity because it needs early diagnosis to treat.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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