Rituximab combined with Bruton tyrosine kinase inhibitor to treat diffuse large B-cell lymphoma in elderly patients: Two case reports

Rituximab combined with BTKI to treat diffuse large B cell lymphoma

Abstract

BACKGROUND
Diffuse large B-cell lymphoma (DLBCL) is a common aggressive non-Hodgkin's lymphoma (NHL), accounting for 30-40% of adult NHL. The purpose of this study was to explore the efficacy and safety of rituximab combined with Bruton tyrosine kinase inhibitors (BTKis) in the treatment of elderly patients with DLBCL.

CASE SUMMARY
The clinical data of 2 elderly patients with DLBCL who received rituximab combined with BTKi in our hospital were retrospectively analyzed, and the literature was reviewed. Two elderly patients with diffuse large B-cell lymphoma were treated with the R-miniCHOP regimen for 2 courses of chemotherapy. Then, they received rituximab in combination with BTKi.

CONCLUSION
The treatment experience in these cases demonstrates the potential ability of rituximab combined with BTKi to treat elderly DLBCL patients, thus providing a new treatment strategy.
**Key Words:** Diffuse large B-cell lymphoma; Rituximab; Bruton tyrosine kinase inhibitors; Elderly patients; Case report

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**Core Tip:** The clinical data of 2 elderly patients with DLBCL who received rituximab combined with BTKi in our hospital were retrospectively analyzed, and the literature was reviewed. Two elderly patients with diffuse large B-cell lymphoma were treated with the R-miniCHOP regimen for 2 courses of chemotherapy. Then, they received rituximab in combination with BTKi. The treatment experience in these cases demonstrates the potential ability of rituximab combined with BTKi to treat elderly DLBCL patients, thus providing a new treatment strategy.

### INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma (NHL), representing 20% – 30% of NHL, and affecting patients with a median age of 66–70 years\[^{1-2}\]. The incidence and mortality of DLBCL increase with age. It was found that the poor prognosis of elderly DLBCL patients is due to the inability to receive standard treatment due to decreased physical function, increased complications, and impaired organ function. Moreover, there are more adverse biological characteristics in elderly DLBCL patients, so the prognosis of elderly DLBCL is often worse\[^{3}\]. Therefore, the treatment of elderly DLBCL patients needs individualized selection, and safety and effectiveness must be considered to achieve reasonable stratified treatment. This paper retrospectively analyzed the diagnosis and treatment of two cases of rituximab combined with BTKI in elderly DLBCL patients, which provided a reference for the treatment of elderly DLBCL patients.
CASE PRESENTATION

Chief complaints

Case 1: The patient complained of right backside and leg pain.

Case 2: The patient complained of epigastric pain.

History of present illness

Case 1: On April 10, 2021, an 86-year-old male patient went to our hospital due to right backside and leg pain for two weeks. Right iliac bone puncture pathology showed DLBCL (non-GCB). Immunohistochemistry included the following: CD20+, PAX5+, CD10-, Bcl-6+, MUM1+, C-myc+ (approximately 40%), Ki-67+ (80%), CD3-, CD5-, CD30-, AE1/AE3-, and SALL4-. Molecular in situ hybridization was EBER-negative.

Case 2: On May 21, 2021, an 87-year-old female patient went to our hospital due to epigastric pain for one week. On May 23, 2021, the gastroscope showed a giant ulcer in the stomach. Pathology showed DLBCL (GCB). Immunohistochemistry included the following: CD20 (+), PAX5 (+), CD3 (-), CD5 (-), Ki-67+ (90%), CD10+ (5%), Bcl-2+ (30%), Bcl-6+ (80%), C-Myc+ (70%), MUM1 (-), CyclinD1 (-), CD21 (-), CD23 (-), AE1/AE3 (-), CK19 (-), and EBER (-).

History of past illness

Two patients had no family history and no specific social history.

Personal and family history

No personal or family history was available.

Physical examination

Case 1: Physical examination showed that the neck, armpit and groin were enlarged, with no palpable organomegaly or cutaneous lesions.
Case 2: Physical examination showed no palpable lymph nodes, organomegaly, or cutaneous lesions.

**Laboratory examinations**
The peripheral blood and biochemical parameters (liver and renal function and serum lactate dehydrogenase level) were within normal limits. Bone marrow (BM) smear and biopsy did not show evidence of lymphoma cell involvement.

**Imaging examinations**
Case 1: On April 12, 2021, PET-CT showed multiple enlarged lymph nodes in the left neck and left supraclavicular region, significantly increased FDG metabolism and a high standard uptake value (SUV) with a Deauville score of 22.3. The bone density of the right ilium increased unevenly, with an irregular soft tissue mass involving the right side of the sacrum and the right acetabulum, with unclear borders (approximately 12.8×11.3 cm) and an uptake value (SUV) with a Deauville score of 11.9. Enlarged lymph nodes were noted in the right paraaortic, retroperitoneal, and perimesenteric vessels, and the uptake value (SUV) had a Deauville score of 10.0 (Figure 1 A-C).

Case 2: On May 22, 2021, PET-CT showed extensive irregular thickening of the stomach wall from the cardia, and the stomach body was accompanied by multiple ulcers, with an uptake value (SUV) and a Deauville score of 23.2 (Figure 2 A-B).

**FINAL DIAGNOSIS**
Based on the above findings, the clinical diagnosis in both cases was diffuse large B-cell lymphoma (DLBCL), stage IVB.

**TREATMENT**
Case 1: After diagnosis, the patient was given the R-miniCHOP regimen for two cycles (rituximab 0.6 g d0, ifosfamide 1 g d1-2, liposomal doxorubicin 20 mg d1, vindesine 4 mg d1, dexamethasone 5 mg d1-5). Efficacy evaluation was assessed as partial remission (PR). The patient developed a severe pulmonary infection after chemotherapy. Then, the patient was given an R-R regimen for six cycles (rituximab 0.6 g d0, ibrutinib 160 mg bid po).

Case 2: On May 28, 2021, the patient was treated with rituximab and dexamethasone (rituximab 0.4 g d0, dexamethasone 5 mg d1-5). On June 23, 2021, the patient adhered to the R-miniCHOP regimen for two cycles (rituximab 0.4 g d0, cyclophosphamide 300 mg d1, liposomal doxorubicin 15 mg d1, vindesine 4 mg d1, dexamethasone 5 mg d1-5). Then, the patient could not continue because of chemotherapy side effects. The patient adhered to an R-R regimen for three cycles (rituximab 0.4 g d0, ibrutinib 160 mg bid po).

OUTCOME AND FOLLOW-UP

Case 1: After treatment, PET-CT showed complete remission of lymphoma (Figure 3). Next, maintenance therapy with zeputinib was continued.

Case 2: PETCT showed complete remission of lymphoma (Figure 4). Then, maintenance therapy with zeputinib was continued.

DISCUSSION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), representing 20% - 30% of NHLs, with a median age of onset of 66-70 years[1-2]. The incidence and mortality of DLBCL increase with age. The poor prognosis of elderly DLBCL is due to the patients’ inability to receive standard treatment due to decreased physical function, more complications, and impaired organ function. Moreover, there are more adverse biological characteristics of elderly DLBCL patients, so the prognosis of elderly DLBCL is often worse[3]. Therefore, the treatment of elderly
DLBCL patients needs to be individualized, and safety and effectiveness must be considered to achieve reasonable stratified treatment. This paper retrospectively analyzed the diagnosis and treatment of two cases of rituximab combined with BTKI to treat elderly DLBCL patients. Our experience provides a reference for the treatment of elderly DLBCL patients.

DLBCL is an extremely aggressive B-cell lymphoma. It has obvious heterogeneity and drug resistance and has a variable prognosis[4]. DLBCL patients over 80 years are defined as ultra-aged DLBCL patients, and there are few reports on them. Ultra-aged DLBCL patients cannot tolerate standard-dose chemotherapy due to various complications and organ dysfunction. The biological characteristics of ultra-aged DLBCL patients also underlie the poor prognosis of the disease, which is characterized by poor response to chemotherapy and easy relapse. The expression of complex karyotypes, poor prognosis genes, and multidrug resistance genes also prevents elderly DLBCL patients from achieving satisfactory results[5]. The treatment of ultra-aged DLBCL patients is still controversial. Ultra-aged patients have less chance of having an autologous HSCT, and traditional treatment has poor efficacy for elderly patients. Therefore, relapse-free survival (RFS) and overall survival (OS) remain low in such patients.

The current standard first-line treatment for DLBCL is the R-CHOP regimen, which can significantly improve OS and progression-free survival (PFS). With this regimen, 30-40% of patients progress to refractory relapsing DLBCL, which has a poor prognosis[6]. One study showed that after R-miniCHOP treatment, the ORR of elderly patients was 63%, with a CR rate of 56% and a PR rate of 7%. The main cause of death of patients was tumor progression, and most adverse events occurred in patients within 2 treatment cycles[7]. Hounsome et al found that among DLBCL patients ≥80 years old, there was no significant difference in the 3-year OS rate between R-miniCHOP and R-CHOP, both of which were approximately 54%.8. Our two elderly patients (age ≥85 years old) started to adhere to the R-miniCHOP regimen. However, it is not effective, and severe myelosuppression and lung infection after chemotherapy require adjustment of the treatment regimen.
With the study of biological characteristics and targeted drugs for DLBCL, a variety of new drugs have appeared continuously. BTKi is a new targeted drug that can inhibit the upstream signaling pathway of the B-cell receptor, thereby inhibiting NF-κB kinase and leading to DLBCL cell death. BTK is a signaling molecule downstream of the B-cell receptor (BCR). It is a key effector molecule that is involved in all aspects of B-cell development and many signaling pathways of B cells, including chemokine receptors and Toll-like receptors (TLRs). BTK is essential for the survival of various B-cell malignancies, such as DLBCL, mantle cell lymphoma, and chronic lymphocytic leukemia, which makes BTK inhibitors valuable drugs to treat B-cell malignancies. BTKi has shown positive efficacy in the treatment of chronic lymphocytic leukemia and mantle cell lymphoma, but there are few reports on the treatment of invasive lymphoma. A clinical trial reported that 80 RR DLBCL patients treated with BTKi had a median age of 60 years, an ORR of 5%, and median overall survival and progression-free survival of 6.41 and 1.64 mo, respectively, and patients with non-GCB had higher rates of partial response and complete response in the GCB subtype than in the GCB subtype.

The most common adverse effect of BTKi is cardiotoxic manifestations, with atrial fibrillation being the most common type. Jennifer R et al found that atrial fibrillation (AF) is usually controllable with continuous BTKi and that the risk factors for supraventricular arrhythmia after BTKi treatment include advanced age, male sex, a history of supraventricular arrhythmia, hypertension and preexisting heart disease. Joseph J et al found that half of the patients who received BTKi had bleeding events. The most common bleeding manifestations are subcutaneous or mucosal, including nasal bleeding, skin ecchymosis, hematuria, etc., and the incidence of fatal bleeding is less than 1%. Other adverse reactions also include infection, diarrhea, and hematological toxicity. Compared with traditional chemotherapy, BTKi is safer. In the process of treatment, we should closely monitor the population with these high-risk factors and actively treat symptoms, and fewer adverse reactions will occur. In this paper, two superelderly patients treated with rituximab combined with BTKi achieved good outcomes, and no serious adverse reactions occurred.
CONCLUSION

For ultra-aged patients, BTKi combined with rituximab is safe and reliable. They cannot tolerate chemotherapy, so new treatment ideas are needed. Our center will continue to treat older patients with DLBCL and explore the feasibility of BTKi plus rituximab in the hopes of finding new treatment strategies for this population.
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