



## Excellent response of rituximab and bendamustine in elderly patient with relapsed diffuse large B-cell lymphoma: a case report

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### ABSTRACT

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Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is currently the most widely used first-line therapy for aggressive B-cell lymphomas. However, many patients, including those with organ dysfunction, may not tolerate the toxicities associated with this regimen. Recent data from the phase III study group indolent lymphomas (StiL) non-Hodgkin lymphoma (NHL)-1 trial suggested that bendamustine plus rituximab were superior in effectiveness and tolerability compared to R-CHOP in the treatment of indolent and mantle cell lymphomas. Preliminary study has indicated the effective use of bendamustine alone or in combination in the treatment of aggressive B-cell lymphomas as well. A 70-year-old male with heavily treated relapsed diffuse large B-cell lymphoma (DLBCL) showed complete remission (CR) after receiving 8 cycles of rituximab in combination with bendamustine as 3<sup>rd</sup> line treatment. Bendamustine has demonstrated considerable efficacy and well-tolerated therapy in relapsed DLBCL patients. Our case report demonstrated that treating patients with bendamustine-based regimen, even in the setting of organ impairment and elderly is safe and effective. Given the increasing evidence of its effectiveness, further investigation of bendamustine's safety and tolerability aspects in special groups is recommended such as those with renal impairment.

### ABSTRAK

Rituximab yang dikombinasikan dengan siklofosfamid, doksorubisin, vinkristin, dan prednison (R-CHOP) merupakan terapi lini pertama yang paling banyak digunakan untuk limfoma sel-B agresif. Namun, banyak pasien, termasuk mereka yang mengalami disfungsi organ, tidak mentolerir efek toksik terkait dengan rejimen ini. Data terbaru dari kelompok studi fase III limfoma yang berkembang lambat (StiL) *non-Hodgkinlymphoma* (NHL)-1 menunjukkan bahwa bendamustine plus rituximab lebih efektif dan ditolerir dibandingkan R-CHOP dalam pengobatan sel limfoma yang berkembang lambat dan mantel sel limfoma. Penelitian pendahuluan menunjukkan efektivitas penggunaan bendamustine secara tunggal atau kombinasi dalam pengobatan limfoma sel B yang agresif. Seorang laki-laki berusia 70 tahun dengan limfoma sel B besar (DLBCL) menunjukkan remisi lengkap (CR) setelah menerima 8 siklus rituximab dalam kombinasi dengan bendamustine sebagai pengobatan lini ke-3. Bendamustine menunjukkan efektivitas yang cukup besar dan ditoleransi dengan baik pada pasien DLBCL yang kambuh. Laporan kasus kami menunjukkan bahwa terapi pasien DLBCL dengan rejimen berbasis bendamustine efektif dan aman, bahkan pada pasien usia lanjut dengan gangguan fungsi organ. Mengingat semakin banyak bukti efektivitasnya, penelitian lebih lanjut tentang keamanan dan tolerabilitas bendamustine pada kelompok khusus direkomendasikan, seperti pasien dengan gangguan ginjal.

### Keywords:

diffuse large B-cell lymphoma;  
first line therapy; relapsed;  
rituximab and bendamustine;  
complete remission;

## INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) which commonly occurs in older patients, with median age of 70 years at diagnosis.<sup>1,2</sup> The combination of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the standard first line treatment regimen in patients with CD20+ DLBCL. However, most of the evidence supporting the use of R-CHOP apply to patients younger than 80 years with limited comorbidities, thus many of the elderly and frail patients might be classified as unsuitable for this regimen.<sup>3-5</sup> Furthermore, many of the reduced-dose variant of this regimen still associated with intolerable toxicities for elderly.<sup>4,6,7</sup>

Bendamustine is a worldwide approved cytotoxic alkylating agent and used for treating a number of lymphoid malignancies (chronic lymphocytic leukemia and other indolent NHL) in Europe and the US.<sup>8</sup> The drug consists of an alkylating nitrogen mustard group bound to a purine-like benzimidazole ring.<sup>9-11</sup> Preclinical studies and clinical observations suggested that bendamustine has limited cross-resistance with other alkylating agents. In addition, it demonstrates significant synergism with anti-CD20 monoclonal antibody rituximab and purine analogues.<sup>12,13</sup> Based on two multicenter randomized studies, bendamustine has received approval for second-line therapy in relapsed/refractory indolent NHL.<sup>11,14</sup>

A growing body of evidence suggested good efficacy and acceptable tolerability of bendamustine as the first-line option for indolent lymphoma, mantle cell lymphoma (MCL), and selected patients with aggressive lymphoma.<sup>15,16</sup> Consequently, bendamustine-rituximab (BR) was tested in DLBCL patients, initially in relapse/

refractory settings and then also as first-line treatment.<sup>17-19</sup> Here we reported the safe and effective use of bendamustine in combination with rituximab for second relapse DLBCL case in a frail elderly with several comorbidities who received prior R-CHOP treatment.

## CASE REPORT

In January 2011, a 72-years-old male presented with enlarged cervical mass with B symptoms for 2 months (FIGURE 1). Biopsy of the mass was performed and he was diagnosed with Ann Arbor stage 3, CD20 (+), high grade DLBCL. His baseline LDH was 675 with performance status of class 1 eastern cooperative oncology group (ECOG). During March until September 2011, he was treated with 8 cycles of R-CHOP chemotherapy every 3 weeks, which comprised of rituximab 375 mg/m<sup>2</sup>, cyclophosphamide 750 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup>, and prednisone 80 mg/m<sup>2</sup>. He achieved complete response upon completion of chemotherapy. Six years later he experienced locoregional recurrence and was treated with 3 cycles R-CHOP chemotherapy. He did not receive full regimen of 6 cycles due to worsening of renal function after the third cycle (glomerular filtration rate of 33 mL/min/1.73 m<sup>2</sup>). Nevertheless, he achieved complete response after 3 cycles of R-CHOP.

In June 2019, he experienced second locoregional recurrence and was prescribed a third line chemotherapy regimen of bendamustine 90 mg/m<sup>2</sup> and rituximab 375 mg/m<sup>2</sup> (FIGURE 2). The patient experienced no adverse event and achieved complete remission (CR) after 8 cycles of chemotherapy (FIGURE 3). The patient remained in CR at 7-month post treatment follow-up (FIGURE 4).

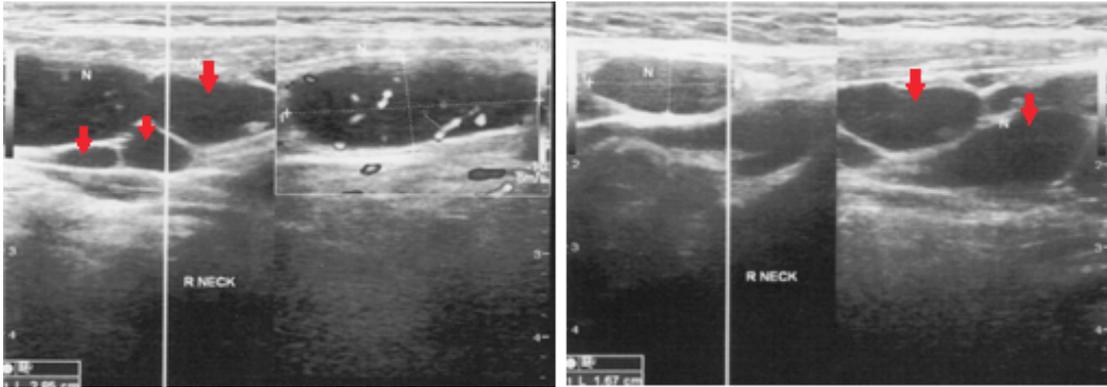


FIGURE 1. Cervical ultrasonography performed before initiation of rituximab-bendamustine in May 2019. Multiple enlarged cervical lymph nodes were observed on right mid-jugular (left) and right-supraclavicular (right) cervical region.

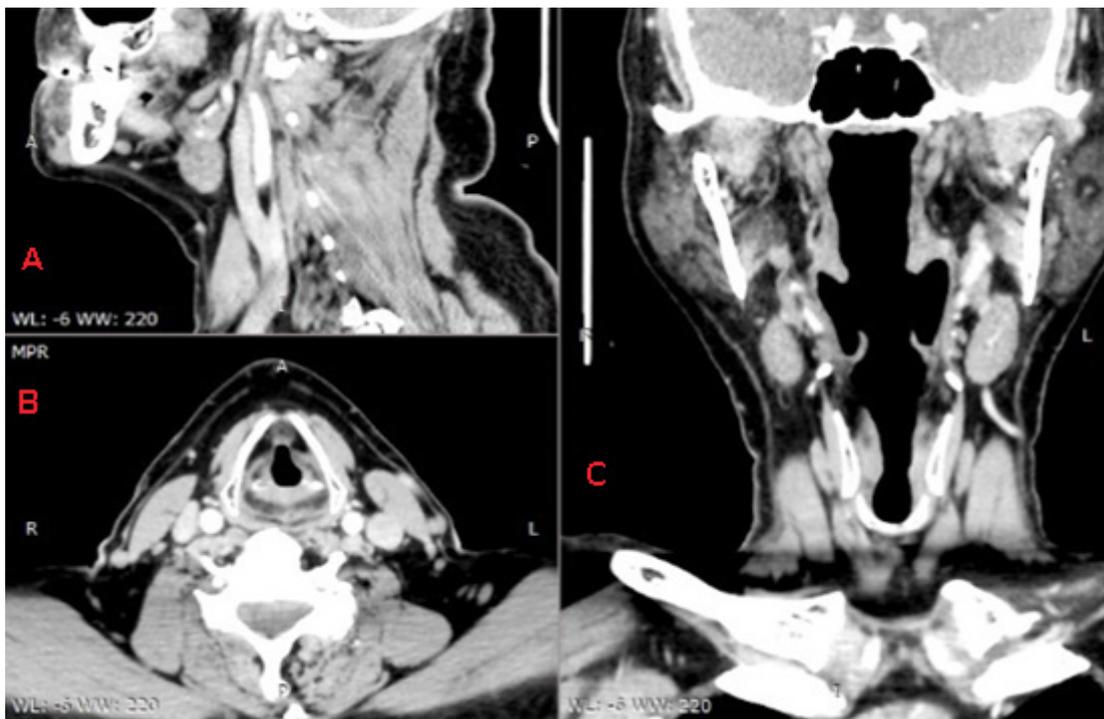


FIGURE 2. Sagittal (a), transverse (b), and coronal (c) view of cervical MSCT performed after 8 cycles of BR (May 2020) revealed no evidence of lymph node enlargement.



FIGURE 3. Sagittal (a), transverse (b), and coronal (c) view of cervical MSCT performed 7 months after completion of BR (August 2020) revealed no evidence of lymph node enlargement.

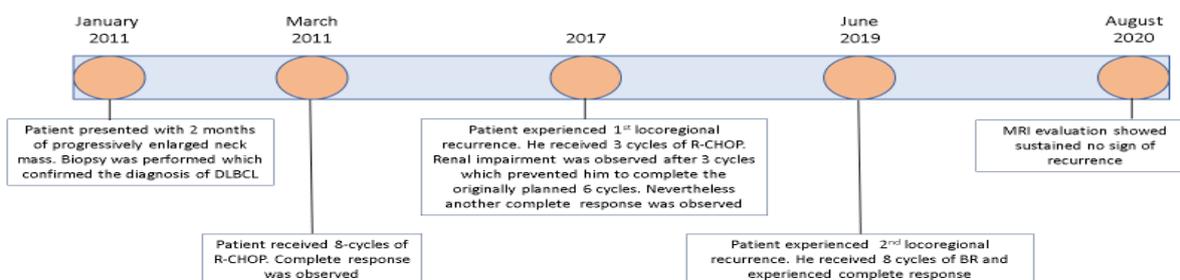


FIGURE 4. Timeline showing patient's course of disease.

## DISCUSSION

We reported a case of relapsed DLBCL in frail elderly patient who achieved CR after 8 cycles of rituximab and bendamustine. He had sustained remission with no sign of disease recurrence at 7 months follow-up.

Treatment outcomes for DLBCL

patients have significantly improved since the introduction of R-CHOP regimen. However, up to 40% of patients with DLBCL do not achieve durable remission, requiring multiple lines of chemotherapy regimens.<sup>10,14</sup> Unfortunately, standard therapies, such as R-CHOP and rituximab, cyclophosphamide, vincristine, and

prednisone (R-CVP) are associated with multiple toxicities such as peripheral neuropathy, cardiac toxicities, myelosuppression, and alopecia. This presents a challenge in elderly patients which have decreased physiologic function and might not be able to tolerate side-effects associated with R-CHOP. Our patient showed excellent response towards the first cycle of R-CHOP without any noticeable adverse event. He received another cycle of R-CHOP after the first locoregional recurrence and showed another CR. We chose to re-prescribe R-CHOP for this patient due to his extended period of remission (6 years) before recurrence, unfortunately he experienced renal function deterioration which prevented him from receiving full cycle.<sup>16</sup>

Bendamustine-based regimens, such as BR, can be considered as an option in the management of relapsed DLBCL. In randomized phase 3 clinical trials, bendamustine in combination with rituximab demonstrated efficacy and acceptable safety profiles compared with standard frontline regimens for indolent B cell NHL and mantle-cell lymphoma (the StiL study and the BRIGHT study).<sup>12-15</sup> Hammersen *et al.*<sup>20</sup> in retrospective analysis confirms R-B and R-mini-CHOP as reasonable treatment options for 1<sup>st</sup> line treatment of elderly and comorbid DLBCL-patients. Toxicity was well manageable in both treatment arms. Superior hematologic tolerability of R-B compared to R-mini-CHOP warrants a treatment recommendation in particular for patients with impaired hematologic reserve.<sup>21</sup> Hong *et al.*<sup>22</sup> confirmed the high efficacy and acceptable toxicity profile of BR in relapsed or refractory DLBCL patients in multicenter retrospective analysis of 58 patients. The median progression free survival was 3.9 months (95% confidence interval [CI]: 2.4–5.4 months), and the median overall survival was 6.7 months (95% CI: 4.7–8.7 months).<sup>22</sup> Increasing interest in

BR as an upfront therapy has prompted a cost effectiveness analysis of this drug. When compared to RCHOP or RCVP regimens, the BR was found to be cost-effective, and due to its more favorable toxicity profile it incurred lower costs related to adverse event management. Therefore, BR seems to possibly evolve to a therapeutic option in frail or slow-go DLBCL patients.<sup>9,12,18</sup>

## CONCLUSION

We observed excellent response and tolerability of bendamustine-rituximab regimen given to relapsed elderly DLBCL patient. Given the increasing evidence of its effectiveness, further understanding of bendamustine's safety and tolerability in special population, such as those with renal impairment, is crucial.

## ACKNOWLEDGMENT

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