Clinical Case Report

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Can early switch to rituximab-bendamustine in a patient with follicular non-Hodgkin lymphoma progressing during R-CHOP be considered frontline treatment?

A case report

Claudio Cerchione, MD, PhD[a,*], Davide Nappi, MD[b], Gerardo Musuraca, MD[a], Alessandro Lucchesi, MD[a], Ilaria Cimmino, PhD[c], Fabrizio Pane, MD[d], Amalia De Renzo, MD[d], Giovanni Martinelli, MD[a]

Abstract

Rationale: Follicular non-Hodgkin lymphoma (fNHL) is a neoplasm characterized by an indolent course and chemosensitivity, but also by disease recurrence. Bendamustine is often used as frontline treatment or second line.

Heading diagnosis: fNHL.

Patient concerns: A 63-year-old Caucasian male with diagnosis of fNHL lymphoma underwent to cyclophosphamide, doxorubicin, vincristine, and prednisone associated with rituximab chemoimmunotherapy, during which interim reevaluation showed progressive disease and severe toxicity.

Interventions: Early switch to rituximab-bendamustine.

Outcomes: This regimen was well tolerated, patient compliance was optimal, there were no delays in administration and no infectious episodes. An interim reevaluation after 3 courses revealed that the patient was fit, the blood cell count was normal, and lymphadenopathies and nocturnal sweating had completely regressed. Of note, the PET/CT scan did not show fluorodeoxyglucose pathological uptake, clearly confirming disease regression.

Lessons: Early switching to a bendamustine-rituximab-based scheme, even during conventional chemotherapy, decreases toxicity and reduces the risk of treatment interruption or delay, with favorable effects on overall response and prognosis.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone, fNHL = follicular non-Hodgkin lymphoma, R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone associated with rituximab.

Keywords: bendamustine, early switch, non-Hodgkin lymphoma, pegfilgrastim, R-CHOP, rituximab

1. Introduction

Follicular non-Hodgkin lymphoma (fNHL) is the most common type of non-Hodgkin lymphoma in the United States and Europe. It is a heterogeneous group of indolent and slow-growing neoplasms which, although showing significant chemosensitivity to conventional frontline treatments, are characterized by recurrence. The most widely used frontline chemotherapy scheme is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) associated with cyclophosphamide, doxorubicin, vincristine, and prednisone associated with rituximab (R-CHOP),

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[a] Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, [b] Department of Hematology and CBMT, Ospedale di Bolzano, Bolzano, [c] Department of Translational Medicine, Federico II University of Naples, [d] Hematology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy.

[*] Correspondence: Claudio Cerchione, Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via P. Maroncelli 40, 47014 Meldola, Italy (e-mail: claudio.cerchione@irst.emr.it).

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but rituximab-bendamustine has become an alternative frontline option for many patients.[1] Italian and European guidelines for second-line therapy consist in different options, among which bendamustine can be used as a single agent or in combination with others.[2,3] Here, we describe the case of a 63-year-old patient with fNHL who was switched to rituximab-bendamustine as early second-line treatment after 2 courses of R-CHOP, interrupted because of hematological toxicity and signs of progressive disease. This strategy resulted in complete disease remission, highlighting the effectiveness of the early switch to a bendamustine-based regimen, even during disease progression.

2. Case presentation

A 63-year-old Caucasian male was referred to our Hematology Unit because of multiple superficial lymphadenopathies, a 5-kg weight loss in the previous 3 months, anorexia, itching, and copious nocturnal sweating. The patient's general conditions were fairly good and his past medical history was negative. Clinical examination confirmed several lymphadenopathies (up to 3 cm), mild hepatomegaly and notable splenomegaly (20 cm). A complete blood count revealed leukocytosis with lymphocytosis and a blood smear showed small lymphocytes with thickened chromatin and scant cytoplasm. Flow cytometric analysis was positive for CD20, CD10, and CD5. An ^{18}F-FDG (fluorodeoxyglucose) PET/CT scan (Fig. 1) showed and accumulation of FDG in several deep and superficial lymph node locations (standardized uptake value (SUV) max range 2–7.7). Excisional biopsy of the largest lymph node in the left axillary region led to a diagnosis of fNHL, stage IV B, CD20+ and bcl-2+. The histological exam showed substantial lymphocytic infiltration (about 82% of the total cell population), while flow cytometry was positive for CD19, CD20, CD10, and k-chains. Conventional frontline treatment with the R-CHOP scheme (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) was planned together with supportive therapy consisting in growth factors (pegfilgrastim and erythropoietin β administered from the first cycle onwards). The second course was deferred because of hematological adverse events, that is, common terminology criteria for adverse events grade III anemia and febrile neutropenia, initially treated with ciprofloxacin per os and then substituted with ceftriaxone as fever persisted. After the third cycle of R-CHOP, clinical and instrumental interim reevaluation showed progressive disease. Systemic B-symptoms were still reported by the patients and lymph-nodes were unmodified at clinical evaluation. ^{18}F-FDG-PET/CT showed no substantially changes in lymphadenomegaly volumes. The frontline regimen was thus interrupted and switched to bendamustine-rituximab (rituximab 375 mg/m^2 on day 1 and bendamustine 90 mg/m^2 on days 1–2) supported by growth factors (pegfilgrastim 6 mg on day 4[4–9] and erythropoietin β 30,000 U/wk, administered from the first cycle onwards), every 28 days for 6 courses. This regimen was well tolerated, patient compliance was optimal, there were no delays in administration and no infectious episodes. An interim reevaluation after three courses revealed that the patient was fit, the blood cell count was normal, and lymphadenopathies and nocturnal sweating had completely regressed. Of note, the ^{18}F-FDG PET/CT scan did not show FDG pathological uptake, clearly confirming disease regression (Fig. 2).

3. Discussion

R-CHOP is a consolidated chemotherapeutic scheme widely used as frontline treatment for fNHL. There are several second-line options for refractory or relapsed disease among which bendamustine is utilized as a single or combined agent. Our

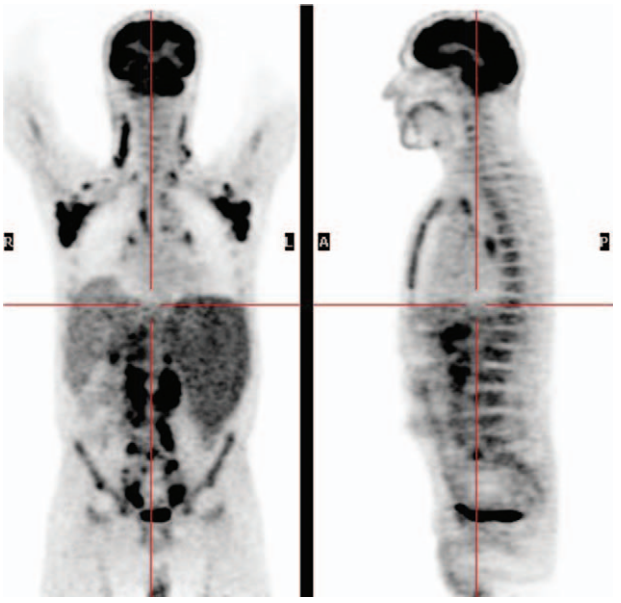

Figure 1. Positron emission tomography/computed tomography scan at diagnosis showed accumulation of fluorodeoxyglucose in several deep and superficial lymph node locations (SUV max range 2–7.7).

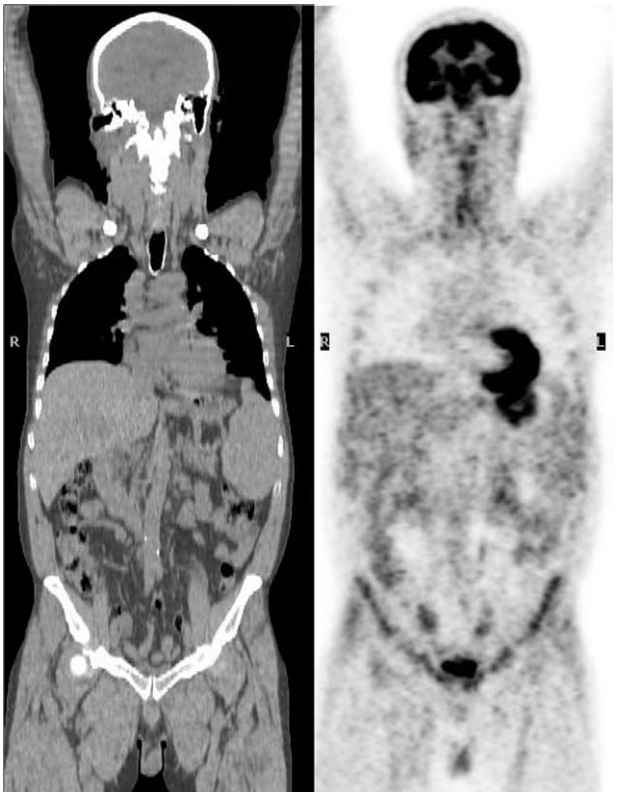

Figure 2. Reevaluation positron emission tomography/computed tomography scan revealed no fluorodeoxyglucose pathological accumulation, confirming clear disease regression.

decision to suddenly switch to another chemotherapy regimen was made by clinical findings (no response to frontline treatment), data from literature and, finally, to our clinical experience in mitigate side effects of bendamustine. Response rates with bendamustine in refractory/relapsed patients after a frontline therapy are excellent and well tolerated, with a 90% overall response rate, a complete response rate of up to 69% and progression-free survival of 23 months.[1,10–14]

The 2 regimens, R-CHOP and bendamustine-rituximab, were directly compared by Rummel et al in a randomized trial evaluating patients with indolent lymphomas, revealing an advantage for the bendamustine-rituximab scheme in terms of median progression-free survival (69.5 vs 31.2 months, respectively) and tolerability (lower rates of grade 3–4 neutropenia in the former).[15] Another study (BRIGHT trial) confirmed the noninferiority of bendamustine over R-chemotherapy regimens (R-CHOP, R-CVP (Rituximab- C – cyclophosphamide, V – vincristine, P – prednisolone)) in terms of effectiveness as first-line treatment in this setting.[16] Thus, despite the lack of difference in long-term overall survival (OS), bendamustine would seem to be a better choice for patients who are more likely to be susceptible to the toxic effects of more intensive combination treatments such as the elderly or those with numerous comorbidities.

During frontline therapy with R-CHOP, our patient experienced substantial hematological toxicity resulting in severe anemia and neutropenia, even though growth factors were used. In particular, our group has previously demonstrated that primary prophylaxis with pegfilgrastim during bendamustine-containing therapy is more effective than secondary prophylaxis with non-pegylated granulocyte colony-stimulating factors in increasing tolerability and in helping to respect dose-density and dose-intensity, regardless of the type, biology and clinical behavior of the lymphoproliferative disease, for example, lymphoma and multiple myeloma. Severe febrile neutropenia was present, but the short duration and the relatively benign course did not necessitate treatment disruption, allowing us to switch to a more tolerable regimen for the patient.

There is still no clear evidence in the literature of the effectiveness of early treatment switching in patients with indolent lymphomas who relapse or experience severe toxicity whilst undergoing R-CHOP. However, in our patient early second-line treatment with rituximab-bendamustine was well tolerated, obtaining results that make it a potentially effective option for patients with early refractory or relapsed fNHL after frontline therapy, or even for those progressing on conventional chemotherapy. We conclude that early switching to a bendamustine-rituximab-based scheme, even during conventional chemotherapy, decreases toxicity and reduces the risk of treatment interruption or delay, with favorable effects on overall response and prognosis.

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Author contributions

Conceptualization, design and writing: Claudio Cerchione, Giovanni Martinelli.
Clinical and research management: Claudio Cerchione, Davide Nappi, Gerardo Musuraca, Alessandro Lucchesi, Ilaria Cimmino, Fabrizio Pane, Amalia De Renzo.
All authors read and approved the final manuscript.

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