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Retreatment with obinutuzumab: An addition to the therapeutic landscape of chronic lymphocytic leukemia

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Abstract

Obinutuzumab is used for the treatment of chronic lymphocytic leukemia. So far there are no data of using this for retreatment in patients who have received it previously. We introduced obinutuzumab for the retreatment in a chronic lymphocytic leukemia patient, who had first achieved partial remission with it and eventually relapsed over a course of 2.5 years. After retreatment with single-agent obinutuzumab, the patient achieved a partial remission again within one cycle and continues to maintain the response status. This case is a platform for considering obinutuzumab as a viable option for retreatment of chronic lymphocytic leukemia patients who have received it before, similar to the pattern of use for other anti-CD20 monoclonal antibodies in this disease, including rituximab.

Keywords

Hematology, obinutuzumab, retreatment, chronic lymphocytic leukemia

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Introduction

Chronic lymphocytic leukemia (CLL) is a treatable but incurable hematologic malignancy, with recent introduction of several new therapeutic agents.[1,2] Fixed-duration therapy utilizing anti-CD20 monoclonal antibodies (MoAbs) with or without cytotoxic chemotherapy remains a mainstay for CLL treatment, compared with newer targeted agents that usually require indefinite treatment to progression or intolerability. While retreatment with rituximab, a first-generation anti-CD20 MoAb has been reported in relapsed non-Hodgkin lymphomas (NHL),[3] retreatment data with obinutuzumab, the most novel agent in this class is not reported yet, especially in CLL. Overall, obinutuzumab has an acceptable safety profile with mainly grades 1 and 2 adverse events (AEs) and more severe AEs (grades 3–5) being reported relatively infrequently within clinical trials.[4] The three major safety events were infusion-related reactions (IRRs), hematologic AEs, primarily neutropenia and infections.[4] We report clinical experience with retreatment using obinutuzumab after the patient had received it previously, achieved a partial response and subsequently relapsed.

Case

A 65-year-old male, with a past medical history of glaucoma, cataract, squamous cell carcinoma of the right eyelid, hyperplastic polyp and hyperlipidemia, was diagnosed with Rai stage 0 CLL by absolute monotypic B-cell lymphocytosis $>5 \times 10^9$/L on normal peripheral flow cytometry, in the year 2000. He did not have any high-risk markers, with CD38 negative disease that showed del 13q on fluorescent in situ hybridization (FISH) and normal beta-2-microglobulin (B2M) as well as lactate dehydrogenase (LDH). He remained asymptomatic and under observation for several years but was noted to have rapidly increasing lymphocytosis, progressive lymphadenopathy, symptomatic splenomegaly and thrombocytopenia in 2015 (Table 1 and Figure 1). Bone marrow biopsy revealed hypercellular marrow with diffuse

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Table 1. Laboratory findings at various time points during clinical course of the index case.

Laboratory parameter	Normal range	At initial diagnosis (June 2000)	Prior to first obinutuzumab treatment (January 2015)	At end of first obinutuzumab treatment (July 2015)	Prior to obinutuzumab retreatment (September 2017)	After retreatment (January 2018)
WBC ($\times 10^9$/L)	3.5–10.5	13.2	190	7.3	48.1	2.9
ALC ($\times 10^9$/L)	0.9–2.9	9.3	184.3	1.11	42.38	0.83
ANC ($\times 10^9$/L)	1.7–7.0	NA	1.9	5.63	1.41	
Hgb (g/dL)	12–15.5	15.6	13.1	14.2	12.8	14.3
Platelets ($\times 10^9$/L)	150–450	159	86	113	76	89
LDH (U/L)	122–222	152	223	169	183	146
Peripheral flow cytometry	–	Monotypic B-cells	Monotypic B-cells	Too few to be calculated	Monotypic B-cells	Too few to be calculated
MRD	–	NA	NA	0.37%	NA	0.05%
FISH	<7%			13q del	13q del	–
Lymphadenopathy				Yes	N/A	N/A
Splenomegaly				Yes	N/A	N/a

WBC: white blood cell count; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; Hgb: hemoglobin; LDH: lactate dehydrogenase; FISH: fluorescent in situ hybridization; MRD: minimal residual disease; NA: not available.

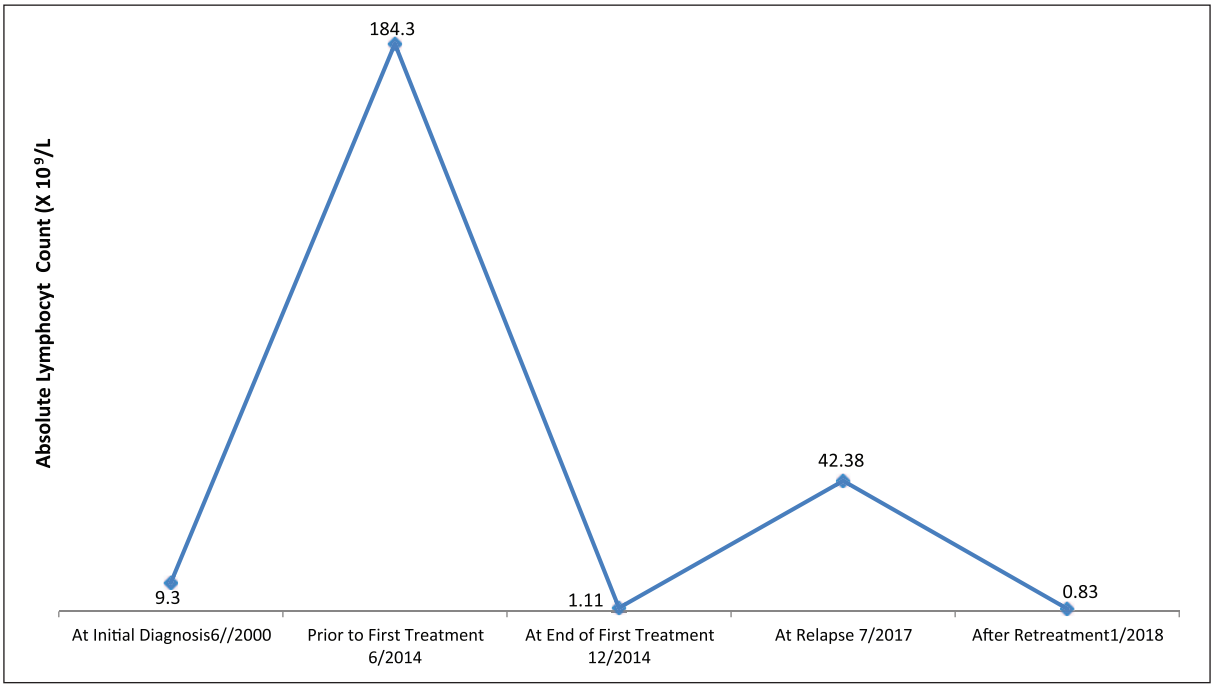

Figure 1. Absolute lymphocyte count at various time points during clinical course of the index case.

involvement by lambda light chain-restricted small lymphocytes occupying 95% of the marrow space. First-line treatment was planned with obinutuzumab (1000 mg) and chlorambucil as per standard guidelines[5] but the patient never started chlorambucil due initially to a concern of tumor lysis syndrome from significant disease burden, and later due to development of prolonged neutropenia and thrombocytopenia on obinutuzumab alone. The dose of obinutuzumab was reduced by 20% for cycle 4 and he was given daily G-CSF for three days after the obinutuzumab dose for that cycle only. After completion of six planned cycles of single-agent obinutuzumab, the patient achieved partial response (PR) to therapy as measured by greater than 50% reduction in absolute lymphocyte count (ALC) and splenomegaly as well as a platelet level greater than 100×10^9/L, as per iwCLL guidelines.[6] Disease was detectable as minimal residual disease (MRD) only, by CLL specific MRD peripheral flow cytometry 0.37%, 2 months after completion of

treatment, without residual blood, spleen or lymphadenopathy detected. His CLL remained stable over the next 2 years with only slight increase in lymphocytosis. Approximately two-and-a-half years after initial treatment, thrombocytopenia and rapid increase in lymphocytosis were noted (Table 1 and Figure 1).

A repeat flow cytometry confirmed monoclonal B-cell population along with an upward trending ALC, confirming disease relapse. A repeat FISH once again showed a 13q deletion. Retreatment was initiated due to worsening fatigue and concern for infections as Absolute neutrophil count (ANC) was trending downward. After discussing several treatment options, a shared decision of reintroducing obinutuzumab was taken based on the prolonged initial response of over 2 years with this as a single agent. Lymphocyte count normalized after only one cycle of retreatment and the patient eventually achieved partial response again per the same iwCLL guidelines.[6] Grade 2 IRR was noted at initial treatment but not at retreatment while grade 2 neutropenia and thrombocytopenia were noted at initial as well as retreatment with obinutuzumab. The patient continues to follow up 1 year after the relapse for surveillance and provided informed consent for reporting.

Discussion

Obinutuzumab is a gylocengineered, humanized type II anti-CD20 MoAb and its combination with chlorambucil is one of the frontline treatment options for CLL patients.[5,7] Obinutuzumab plus chlorambucil had a favorable safety profile (up to 35% of patients with severe neutropenia and up to 12% with severe infections).[5] The Phase1/2 GAUGUIN study showed that monotherapy with obinutuzumab was active in heavily pre-treated relapsed/refractory CLL.[8] The CLL11 trial (NCT01010061) of the German CLL Study Group demonstrated that the anti-CD20 monoclonal antibody obinutuzumab was superior to rituximab. At the same time, a recent study has pointed out potential use of Obinutuzumab as monotherapy in treatment-naïve patients.[4] While retreatment with earlier generation anti-CD20 MoAb, rituximab, is a widespread practice in management of B-cell malignancies, ours is the first report of retreating CLL in the same patient using obinutuzumab and achieving partial response for a second time. The grade 2 IRR which was noted at initial treatment could be attributed to higher ALC as has been suggested by another previous report.[9] Furthermore, obinutuzumab monotherapy induces natural killer cell depletion in the peripheral blood of patients with chronic lymphocytic leukemia and this may be linked to its mechanism of action as well as its pharmacodynamics, but has not yet been fully elucidated.[10] With a longer follow-up, the higher rate of eradication of MRD that has been observed with obinutuzumab as compared with rituximab may have lead to an overall survival benefit and an improvement in progression-free survival.[5] As obinutuzumab is used more frequently in CLL, retreatment may be studied systematically in planned, prospective clinical trials.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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