

Editorial

Primary Refractory Double Hit Diffuse Large B Cell Lymphoma: Complete Response to Ibrutinib and Rituximab

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Double Hit Lymphoma (DHL) associated with translocations in MYC and BCL-2 or BCL-6 gene accounts for approximately 5-10 % of all Diffuse Large B Cell Lymphoma (DLBCL) [1]. These patients are distinct from double-expressers who stain positive on immunohistochemistry for MYC and BCL2 or BCL6 accounting for approximately 25-35% of all DLBCL. Double expresser DLBCL have relatively poor outcomes but DHL is associated with extremely aggressive course and poor prognosis. With R-CHOP, R-EPOCH or similar induction therapy a complete response rates of 30-70% have been reported for DHL with 5 years survival of only 27-36% [2]. Patients with primary refractory DHL have dismal prognosis with limited therapeutic options. Additionally, in absence of chemo sensitivity, these patients are not candidate for high-dose chemotherapy and Autologous Stem Cell Transplantation (ASCT). We herein report a patient who failed multiple chemotherapies but surprisingly had complete pathologic response to Ibrutinib and Rituximab (IR).

Standard lymphoma staging, international prognostic index defined initial diagnosis and RECIST criteria were utilized for lymphoma response [3]. A 62 years old Caucasian male was diagnosed with stage IVB DLBCL (IPI score-4) in February 2013. Cervical node biopsy was positive for C-MYC and BCL-2 translocation with proliferative index of 70%. Bone marrow was involved, CSF was negative, LDH was elevated and he had 40 pounds weight loss with night sweats. Treatment with 4 cycles of rituximab, cyclophosphamide, Adriamycin, vincristine and prednisone (R-CHOP) produced partial response with persistence of PET avid (SUV down to 9 from 17) disease in retroperitoneum that was bulky (17x21 cm). He subsequently received 2 cycles of Rituximab, Ifosfamide, Carboplatin and Etoposide (RICE) and 2 cycles of hyper fractionated Cyclophosphamide, vincristine, adriamycin and dexamethasone (Hyper-Cvad) with stable response and progressive disease respectively (Table 1).

For primary refractory DHL he was started on 560 mg Ibrutinib daily orally along with rituximab weekly x 4 doses then monthly x

6 doses beginning April 2014. Treatment was well tolerated without dose modifications. Kinetics of tumor response is explained in (Table 1). With continued response, ibrutinib was continued for 1 year resulting in reduction of retroperitoneal lymph node to 1.5 x 1 cm and SUV of 2.9. During ASCT, ibrutinib was stopped 7 days preceding stem cell mobilization and 1 day before stem cell infusion. He received high dose therapy with BCNU, Etoposide, Cytosine Arabinoside, Melphalan and Rituximab (BEAMR) followed by 5.67x10⁶ CD 34+ cells rescue in October 2014. Ibrutinib was promptly resumed upon engraftment on day +13. A PET scan in January 2015 revealed increase in size and SUV to 2.4 x 2 cm and 4.6 respectively. In February 2015 he underwent laparoscopic biopsy of this lesion that was negative for DLBCL. Ibrutinib was stopped for 3 days preceding and following laparoscopic surgery to minimize risk of bleeding. In November 2015, PET avidity of this stable lesion (2.4 cm) rose to SUV of 5.3 that persisted in scan performed in March 2016. A laparoscopic biopsy was again negative for DLBCL. All biopsies (2 laparoscopic surgical resection and 1 true cut biopsy of mesenteric mass) revealed fibro adipose and connective tissue fibrosis, chronic inflammation, hemosiderin laden macrophages and multinucleated giant cell reaction with dystrophic calcification. No lymphoid tissues, malignancy or infectious process was identified. PET avidity was likely a result of chronic inflammation. He continued ibrutinib for past 5.5 years (Table 1). His pre ASCT PET scan (1.5x1 cm and SUV of 2.9) likely represented a Complete Response (CR) to IR; however we did not document a pathologic CR at that point. Since all the subsequent biopsies are negative [4-6], it raises the question whether patient achieved complete response to IR alone. PET avidity despite repeated negative biopsies may reflect pseudoprogression in context of Ibrutinib as recently described in follicular lymphoma [7].

In February of 2019 he developed pancytopenia that did not improve with cessation of ibrutinib. Bone marrow biopsy revealed therapy related MDS with 30% diploid blasts with NMP-1 as sole molecular abnormality.

Response to Ibrutinib and rituximab combination in previously heavily treated primary refractory DLBCL is encouraging. An overall response rates of 29-37% has been documented for ibrutinib in relapse refractory DLBCL with mostly non GCB DLBCL patients responding (response rate of 30-40% vs. 5% for GCB DLBCL) [4-6]. In these studies, approximately 10% patients with DLBCL achieved CR with ibrutinib; it is not clear if any of these were DHL. In conclusion, we document marked and durable activity of immunotherapy alone in primary refractory DHL after failing multiple cytotoxic chemotherapy regimens. Ibrutinib likely did not contribute to MDS, an association not yet described.

Table 1: Time line of responses and procedures in a DHL patient.

Timeline	Treatment	Response	Nodal Size	Nodal SUV
Mar-13	None	NA	17x21 cm	23
May-13	RCHOP x 4	Partial response	3.7x2.4 cm	9
Jul-13	RICE x2	Stable response	3.1x2.1 cm	8.8
Aug-13	Hyper cvad x2	Progression	3.8 x1.7 cm	12
Oct-13	IR x3 months	Mixed response	2.2x1.6 cm	19
Mar-14	I x 6 months	Mixed response	1.5 x1.2 cm	11
Jun-14	I x 9 months	Mixed response	1.5 x1.2 cm	10
Sep-14	I x 12 months	Partial response	1.5 x 1.2 cm	4.8
Oct-14	I x 13 months	CRu	1.5x1 cm	2.9
Oct-14	BEAMR & ASCT	NA	NA	NA
Jan-15	I x 15 months	? Progression	2. 4x 2 cm	4.6
Feb-15	Laparoscopic surgery	CR	NA	NA
Nov-15	I x 26 months	? Progression	2.4 x 2 cm	5.6
Mar-16	I x 30 months	Stable response	2. 4x2 cm	5.4
May-16	Laparoscopic surgery	CR	NA	NA
Sep-16	I x 36 months	? Progression	2.0 x 1.7 cm	8.4
Sep-16	Mesenteric biopsy	CR	NA	NA
May-17	I x 44 months	CRu	1.8 x1.7	6.1'
Feb-18	I x 50 months	CR	1.6 x1.6	2.8''
Sep-18	I x 56 months	CR	1.5 x 1.5 cm	2.8 ''
Feb-19	Ix61 months	CR	1.5x1.5	2.8''

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