

Combination of ibrutinib and chemotherapy produced a durable remission in multiply relapsed diffuse large B-cell lymphoma leg type with mutant *MYD88* and wildtype *CD79*

The mutant Myd88L265P protein promotes lymphoma cell survival in diffuse large B-cell lymphoma (DLBCL) by activating NF- κ B via Irak-4. On the other hand, constitutively activated signaling of the B-cell receptor (BCR), encoded by *CD79A/B*, activates NF- κ B via Bruton's tyrosine kinase (Btk). Although the Btk inhibitor ibrutinib has demonstrated remarkable clinical activity in Waldenström's macroglobulinemia (WM), an indolent lymphoma characterized by a very high frequency of the *L265P MYD88* mutation, ibrutinib, as a single agent, has demonstrated limited activity in DLBCL, including no response in 7 DLBCL patients with *L265P MYD88* and wildtype *CD79*.¹ Here, we report a case in which ibrutinib, in combination with chemotherapy, produced durable remission in multiply relapsed cutaneous DLBCL leg type with *L265P MYD88* and wildtype *CD79*. Case Report: A woman in her late 70s presented with numbness and skin nodules on her left foot in the spring of 2013. Subsequently, she developed multiple enlarging skin lesions, severe pain in both legs, and progressive weakness of the left foot. Skin biopsy confirmed the diagnosis of cutaneous DLBCL leg type, with the following immunophenotype: CD20+, CD79a+, CD10-, BCL6+, BCL2+, and Mum1+, which was consistent with the activated B-cell-like (ABC) subtype of DLBCL. Positron emission tomography and computed tomography (PET/CT) scan demonstrated multiple Fludeoxyglucose (¹⁸F) (FDG) avid nodules in the lower extremities and FDG avid thickening of the proximal left S1 nerve, but no lymphadenopathy. MRI of the

spine demonstrated enhancing intrathecal nodular densities, excessive epidural enhancement at the base of the neural canal, and asymmetric thickening and enhancement of the left S1 nerve root. The patient was treated with 1 cycle of R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisone, i.e., "R-CHOP" omitting "O" vincristine due to preexisting left foot drop), with a plan to add lenalidomide as soon as its off-label use was approved by her insurance company. However, lenalidomide was denied; the plan was therefore revised to R-EPCH (rituximab, etoposide, prednisone, cyclophosphamide, and doxorubicin, i.e., "R-EPOCH" omitting "O" vincristine). Because of the abnormal MRI and PET/CT results in the spinal cord and S1 nerve root, these sites were presumed to be lymphoma and treated with high dose intravenous methotrexate, administered after R-CHP/R-EPCH, and intrathecal methotrexate/cytarabine, as part of the upfront treatment. Altogether, the patient received 1 cycle of R-CHP, 5 cycles of R-EPCH, 4 intrathecal injections of methotrexate/cytarabine, and 4 cycles of high-dose intravenous methotrexate. She required no dose reduction of any drugs, except for the planned omission of vincristine. Most of her symptoms had resolved by the time she finished 3 cycles of chemotherapy, with the exception of left foot drop which improved partially. Following completion of 1x R-CHP and 3x R-EPCH, an interim PET/CT scan demonstrated complete response (CR). Another PET/CT was done after all planned chemotherapies were completed in January 2014, again demonstrating CR. She then underwent radiation therapy of the S1 nerve root and completed the treatment by the end of January 2014. However, she relapsed in May 2014 with multiple small skin lesions, which were biopsied and proven to be DLBCL leg type. The patient was not a candidate for transplantation due to advanced age;

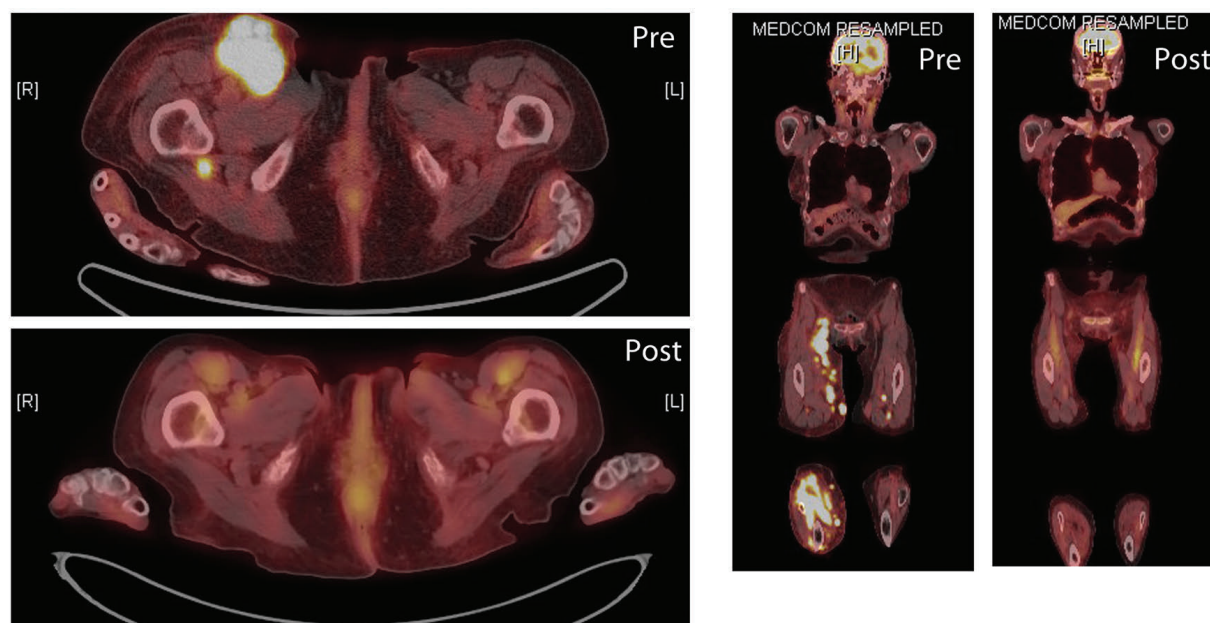


Figure 1. PET/CT images pre- and post-treatment. Patient underwent a PET/CT scan before and after receiving ibrutinib+R-EPOCH x 4 cycles. Images matching the comparable anatomic positions in the coronal and transverse planes were presented.

she therefore enrolled in a phase I clinical trial evaluating TGR-1202, a phosphatidylinositol-3-kinase delta inhibitor. In the first cycle, she clinically had stable disease. In the midst of cycle 2, she developed many skin lesions consistent with her lymphoma. PET/CT results were consistent with progression of disease (POD). The patient then received three cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide), which resolved all the skin lesions and a severely inflamed right 3rd toe. However, she developed new skin lesions before the planned post-treatment week 6 PET/CT. Subsequently, the patient enrolled in a phase I clinical trial evaluating the combination of 5-azacitidine and romidepsin, and had POD during cycle 1. The patient then received two cycles of an off-label therapy comprising liposomal doxorubicin 20 mg/m² on day 1, rituximab 375 mg/m² on day 1, lenalidomide 5 mg daily on days 1-10, and dexamethasone 40 mg on days 1, 8, and 15 on 21-day cycles, and achieved clinically stable disease. However, she developed severe fatigue, dizziness, and hearing loss, all of which were thought most likely to be related to lenalidomide. Finally, she received one cycle of an off-label treatment comprising liposomal doxorubicin 10 mg/m² on days 1 and 8, rituximab 375 mg/m² on day 1, and subcutaneous bortezomib 1.3 mg/m² on days 1 and 8 on a 21-day cycle. However, she had evidence of POD before any further treatment. By April 2015 she had developed, for the first time, large nodal masses in the mediastinum, abdomen, and pelvis, in addition to numerous skin lesions with non-healing large ulcers in the right leg. An ulcer on the right leg was biopsied and confirmed to be DLBCL leg type. At that time, the patient was deteriorating rapidly, and was not a candidate for clinical trials. Since emerging evidence suggested that ABC-DLBCL, compared to the germinal center B-cell (GCB) subtype, may respond to ibrutinib,² we recommended ibrutinib and R-EPOCH to this patient with ABC-DLBCL. The patient was started on R-EPOCH with ibrutinib in April 2015, and achieved a CR with 4 cycles of the regimen (Figure 1). Due to neuropathy, cytopenia, and fatigue, she received 50% dose reduction of vincristine for C1-4, and required 10% dose reduction of cyclophosphamide for C2-4, reduction of ibrutinib from 560 to 420 mg daily for C2-4, and 20% dose reduction of doxorubicin for C3-4. The patient then started maintenance ibrutinib at 560 mg daily in June 2015. In March 2016 she developed severe fatigue, weight loss, and was unable to stand up. Extensive workup for relapse was negative, and she improved after holding ibrutinib for 1 week. She then resumed ibrutinib at 420 mg daily, but had to discontinue it permanently in July 2016 due to severe diarrhea which did not respond to further dose reduction. The patient remains in remission with a negative PET/CT scan in February 2017. To understand any potential mechanisms of this remarkable response, we performed next generation sequencing of 467 genes (http://pathology.columbia.edu/diagnostic/PGM/pdf/cccp_gene_list.pdf) using tumor DNA extracted from the tissues biopsied immediately prior to starting ibrutinib. The results revealed L265P MYD88 and wildtype CD79A/B. Additional mutations were detected in the following genes: B2M, CREBBP, STAT6, CREBBP, GRIN2A, SS18, DOT1L, MEF2B, BARD1, CUL3, EWSR1, KDR, FAT1, FLT4, NOTCH4, CCND3, FAM123B, ATRX, and CIITA. Discussion: The L265P mutant of Myd88 was originally discovered in up to 29% of ABC-DLBCL, and was demonstrated to promote cell survival by activating NF-κB via Irak-4.³ Later, MYD88 L265P was found in

more than 90% of WM.⁴ Although Myd88 L265P activates Btk in WM, there is no such a link (between Myd88 L265P and Btk) in DLBCL.⁵ Clinically, ibrutinib produces a major response in over 90% of WM, probably because the drug blocks Btk signaling, which is otherwise activated by Myd88 L265P. In contrast, the response rate of DLBCL to ibrutinib is low, at 5 and 37% for GCB- and ABC-DLBCL, respectively.¹ Interestingly, none of the 7 patients with MYD88 L265P and wildtype CD79 responded. The patient in this report had multiple relapsed ABC-DLBCL leg type with MYD88 L265P and wildtype CD79, and achieved durable remission, now exceeding 20 months, with the regimen of ibrutinib and R-EPOCH. Given that R-EPOCH in the upfront treatment produced a short-lived remission for this patient, a plausible explanation is that ibrutinib may have acted by overcoming resistance to R-EPOCH in DLBCL cells. Alternatively, ibrutinib as a single agent might similarly produce a favorable response in this patient; a less likely scenario which would suggest that the roles and relationship of Myd88 L265P and Btk may be substantially different in DLBCL leg type *versus* nodal DLBCL, as reported by Wilson *et al.*¹ Ibrutinib has been reported, in a small retrospective study, to produce an encouraging response rate of 50% in primary CNS lymphoma of the non-germinal center subtype,⁷ an extranodal DLBCL known for activated BCR signaling and high mutation rates of MYD88 and CD79.⁸ DLBCL leg type is associated with activated BCR, although the mutation frequencies of MYD88 and CD79 are comparable to nodal DLBCL.⁹ A favorable response to ibrutinib in these entities of DLBCL is likely achievable only when Btk plays a key role in transmitting pathologically dominant BCR signaling; and a poor response to ibrutinib may be expected where BCR signaling is not important or is not transmitted primarily by Btk. However, the exact molecular or genetic predictors for response to ibrutinib, as a single agent or in combination with chemotherapies, remain poorly understood. This challenge highlights the need for more clinical trials. For those patients with relapsed ABC-DLBCL leg type who are not candidates for clinical trials, our results suggest that the combination of ibrutinib and R-EPOCH has the potential to produce durable remission even when mutant MYD88 and wildtype CD79 coexist, and when R-EPOCH has previously failed. In such cases, the dosage and duration of ibrutinib and R-EPOCH need to be determined carefully for individual patients as safety data are lacking.

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doi:10.3324/haematol.2016.161893

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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