Complete Resolution of Extensive Chronic Graft-Versus-Host Disease with Ibrutinib in Relapsed Mantle Cell Lymphoma

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We here in document a complete response of extensive chronic graft-versus-host disease (cGvHD) to a Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib. A 41 year old Caucasian female with stage IVA mantle cell lymphoma (MCL) received four cycles of R-CHOP (rituximab, cyclophosphamide, vincristine and prednisone) and two cycles of RICE (rituximab, ifosphamide, carboplatin and etoposide) without a significant response. Four cycles of bendamustine and rituximab (BR) effected a partial response with persistent PET positive disease. For primary refractory MCL she underwent mismatched unrelated donor allogeneic hematopoietic stem cell transplantation in December 2011 receiving conditioning with cyclophosphamide (60 mg/kg × 2), total body irradiation (1200 cGy), alemtuzumab (10 mg × 3) and total of 6.6 ×10⁶ /kg CD-34+ cells. Tacrolimus is used for graft-versus-host disease (GvHD) prevention. Platelets and neutrophils engrafted on days 11 and 14 respectively and she developed grade III acute GvHD involving the skin and gut on day 17 of transplantation that persisted beyond 100 days post-transplant. Her chronic GvHD (cGvHD) was treated with steroids, but remained active and extensive. Despite active and persistent cGvHD with 100% donor chimerism, in July 2012 she was found to have persistent biopsy proven MCL in the stomach that was treated with external beam radiation (3000 cGy). Subsequent progression in bone marrow and para-aortic lymph nodes in April 2013 was treated with 2 cycles BR with excellent partial response but neurotoxicity precluded continued treatment.

By December 2013, the patient had extensive cGvHD manifesting as scleromatous skin thickening, oral ulcers and sclerosis of the buccal mucosa, ocular dryness and diarrhea. She was started on ibrutinib 560 mg once daily for primary refractory MCL. After two months of therapy, cGvHD had begun to improve. Oral steroids were reduced and ultimately stopped after six months of ibrutinib; after seven months, all cGvHD manifestations resolved completely. A complete remission for MCL was documented at two months of ibrutinib initiation. Currently she continues to be on daily 560mg ibrutinib without cGvHD exacerbation for 34 months; MCL remained in CR for only one year (Figure 1). Overall survival from the initial MCL diagnosis is now 76 months.

Chronic graft versus host disease (cGvHD) is mediated donor T cells. The role of B cells in the pathogenesis of cGvHD is increasingly recognized [1]. In our patient, rituximab given as part of chemotherapy regimen did not improve cGvHD. Two murine studies have explored the role of ibrutinib in cGVHD-like syndromes, one in which there is T cell driven sclerodermatous cGvHD and a second in which there is Ab driven multiorgan system cGvHD that includes Bronchiolitis Obliterans (BO). Administration of ibrutinib decreased the incidence and severity of sclerodermatous, and improved pre-existing lesions and also improved pulmonary fibrosis and reduced BO. Animals lacking BTK and ITK did not develop cGvHD, indicating that these molecules

Figure 1: Timeline for MCL and cGvHD responses (2011 to 2017). (MCL: Mantle Cell Lymphoma; cGvHD: chronic Graft versus Host Disease; AlloSCT: Allogeneic Stem Cell Transplantation; XRT: External beam Radiation; BR: Bendamustine and Rituximab; I: Ibrutinib; CR: Complete Response).
are critical to cGVHD development [2]. Results of an ongoing phase 1b/2 study presented in abstract form reports on eight patients; all five evaluable patients showed partial response (dose determined at 420 mg daily) [3]. In a late breaking session of American Society of Hematology meeting (2016), an overall cGVHD response rate of 67% (sustained for more than 20 weeks in most patients) was presented for ibrutinib in 42 patients [4]. These reports along with ours provide the evidence for ibrutinib mediated cGVHD response and supports ongoing investigations [5].

References


5. Study of the Bruton’s Tyrosine Kinase Inhibitor in Subjects with Chronic Graft Versus Host Disease. Available at: https://clinicaltrials.gov/ct2/show/NCT02195869