Obinutuzumab in combination with high-dose methylprednisolone and concurrent administration of lenalidomide. An effective non-chemotherapy regimen for the treatment of Richter’s transformation

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Patients with chronic lymphocytic leukemia (CLL) who develop Richter's transformation (RT) typically have rapid disease-progress and short survival with current therapies, which also may be poorly tolerated because of myelosuppression. We developed a relatively non-myelosuppressive treatment for such patients based on the apparent sensitivity of lymphoma cells to next-generation anti-CD20 mAb, glucocorticoids, and lenalidomide. Here, we present the results of first two patients treated with a regimen using high-dose methylprednisolone (HDMP), Gazyva-obinutuzumab (G), and lenalidomide (L) prior to allogeneic stem-cell transplantation. This regimen consists of HDMP (1 gm/m²) QD for 5 days at the start of each of 4 cycles (28 days / cycle), G, as per standard dose, and L for 21 days starting on day 6 of each cycle at doses that could escalate with each cycle from an initial dose of 5 mg QD to 20 mg QD, as tolerated. Patient 1 is a 61-year-old female with CLL who presented rapidly progressive left axillary lymphadenopathy. Cytogenetic analysis revealed the presence of del(17p), del(11q) and complex karyotype with multiple translocations. CT/PET scan showed avid FDG-uptake with SUV 10 in left axillary lymph node. Biopsy of an affected node revealed a CD5(+) diffuse large B-cell lymphoma clonally related to her CLL. Patient 2 is a 65-year-old male with CLL previously treated with fludarabine, cyclophosphamide, and rituximab (FCR). He presented with rapidly progressive splenomegaly and lymphadenopathy. CT/PET scan showed FDG uptake in multiple areas. Lymph node biopsy showed atypical mononucleated and multinucleated lymphoid cells consistent with CD20(+) Hodgkin lymphoma (HL). Marrow biopsy showed CLL and HL involvement as well as borderline myelodysplasia. Cytogenetic analysis showed a complex karyotype including del(5q), del(6q), and loss of chromosome 7. FISH showed gain of chromosome 12, 11q, 17p, 13q14.3, LAMP1, and IGH, consistent with tetraploidy. Therapy was well tolerated with grade 1-2 cytopenias that improved with growth factor support. Patients did not develop infections and required no hospitalizations. Patient 1 was able to tolerate a maximum dose of L of 20 mg per day, while patient 2 tolerated a dose of 5 mg daily. Both patients achieved a complete response (CR) as validated by clinical exam, repeat PET/CT, and marrow biopsy. Both elected to proceed with allo-SCT with matched unrelated donors. The conditioning regimen employed fludarabine, melphalan, and ATG, and GVHD prophylaxis with tacrolimus and methotrexate. Both patients developed grade 1-2 GVDH of the skin and GI track that resolved by 6 months post transplant. Both patients remain in CR, now more 12 months after allo-SCT. These cases show that the regimen of HDMP+G+L is active and well tolerated in high-risk patients with RT. Preclinical studies as well as the observations presented here indicate that this non-chemotherapy regimen can overcome the potential chemoresistance that frequently is observed in RT associated with high-risk cytogenetics including del(17p). These highly-encouraging results provide the rationale for a multi-institutional clinical study by the CLL Research Consortium (CRC) that is currently in progress.