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Rajat Bansal, Joseph G. Jurcic, Ahmed Sawas, Markus Y. Mapara & Ran Reshef

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LETTER TO THE EDITOR

Chimeric antigen receptor T cells for treatment of transformed Waldenström macroglobulinemia

Rajat Bansal, Joseph G. Jurcic, Ahmed Sawas, Markus Y. Mapara and Ran Reshef
Division of Hematology & Oncology, Columbia University Irving Medical Center, New York, NY, USA

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Waldenström Macroglobulinemia (WM) is a rare disorder with approximately 1200 new cases diagnosed in the United States every year [1]. It is characterized by a monoclonal IgM gammopathy in the blood, in conjunction with bone marrow infiltration with lymphoplasmacytic cells [2]. WM often has an indolent course before becoming symptomatic. Rarely, patients undergo histological transformation, which portends a more aggressive disease course and a worsened overall survival. Here we describe a patient with relapsed/refractory WM and histological transformation to high-grade B cell lymphoma, which was also refractory. He achieved complete remission (CR) following CD19-targeting chimeric antigen receptor (CAR) T cell therapy without evidence of transformed disease or underlying WM after one year. To our knowledge, this is the first reported case of transformed WM successfully treated with CAR T cell therapy.

This 71-year-old male was diagnosed with WM in 1998, when routine laboratory studies showed elevated serum protein and a monoclonal IgM gammopathy. Serum IgM was elevated to 3940 mg/dL. A bone marrow biopsy at the time of diagnosis showed paratrabecular lymphoid aggregates. Immunohistochemistry and flow cytometry showed monoclonal B-cells with expression of surface IgM and kappa, CD19, CD20, CD7 and CD38. He did not have cytopenias, lymphadenopathy, organomegaly or signs of end organ damage at the time of diagnosis. His International Prognostic staging System for WM (IPSSWM) score was 0 (low risk) [3]. He underwent active monitoring for 12 years, until 2010, when he developed progressive anemia to 9.2 g/dL and splenomegaly to 20 cm. A repeat bone marrow biopsy in 2010 showed hypercellular marrow with multiple paratrabecular aggregates of small lymphocytes with plasmacytoid features. He was treated with six cycles of fludarabine and rituximab from August 2010 to December 2010, and had a partial response. He had improvement in splenomegaly, anemia and decrease in serum IgM (Figure 1).

Four years post therapy, in December 2014, he developed anemia to 10.3 mg/dL, worsening splenomegaly, and an increase in serum IgM level to 1172 mg/dL. A repeat bone marrow biopsy showed lymphoplasmacytic infiltrate comprising 70% of total marrow cellularity. DNA sequencing analysis showed presence of MYD88 L265P mutation. He was treated with 6 cycles of bendamustine and rituximab (BR). In May 2015, prior to cycle 6 of BR, the patient noted left cervical adenopathy. Fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)/CT showed a 3 x 2 cm left cervical lymph node with an SUV of 15.4, and a left thigh lesion with an SUV of 9.9. Biopsy of the left cervical node showed a high-grade B cell lymphoma with MYC and BCL6 rearrangements. Flow cytometry showed a monoclonal B cell population with expression of CD19, CD38, CD43, CD79a, cytoplasmic and surface IgM and surface immunoglobulin kappa, and negative for CD10 expression. Immunoglobulin heavy chain (IgH) gene rearrangement analysis showed the high grade B cell lymphoma to be clonally related to the previously seen lymphoplasmacytic infiltrate, consistent with transformation. Bone marrow biopsy showed involvement by patient’s large cell lymphoma. His International Prognostic Index (IPI) score was 3 (high intermediate-risk). He was then treated with 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with ibrutinib. ibrutinib was added based on early phase data showing high response rates in patients with diffuse large B cell lymphoma, and to treat the underlying WM [4,5]. Post treatment PET/CT showed CR. He continued ibrutinib maintenance after cycle 6 of R-CHOP, but it was discontinued 6 months later due to neutropenia. Bone marrow biopsy in July 2016 showed no overt evidence of a large B-cell lymphoma, but noted a minimal, residual plasmacytic component.

His response lasted for 18 months. In December 2017, he developed anemia to 10.3 mg/dL, worsening splenomegaly, and an increase in serum IgM level to 1172 mg/dL. A repeat bone marrow biopsy showed large B-cell lymphoma involving 10–15% of marrow cellularity. He underwent salvage therapy with 2 cycles of R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), followed by 1 cycle...
of rituximab with high dose cytarabine. PET/CT on Feb 2018 showed a partial response to treatment, and a bone marrow showed no evidence of a large B-cell or lymphoplasmacytic lymphoma.

He subsequently underwent an autologous stem cell transplant in March 2018 with BEAM conditioning (BCNU, etoposide, cytarabine, melphalan). Due to delayed blood count recovery and persistent fevers, he underwent early restaging 1 month after autologous stem cell transplant; PET/CT performed showed progression of disease with multiple new foci of FDG uptake in the spleen and skeleton (Figure 2(a)). A bone marrow biopsy showed extensive involvement by large cell lymphoma, and a residual plasmacytic component. Serum protein electrophoresis showed a monoclonal IgM paraprotein by immunofixation, suggesting progression of the underlying WM. Given chemorefractory disease, he received CD19 targeted CAR T cell therapy with axicabtagene ciloleucel in July 2018 following lymphodepleting chemotherapy with fludarabine and cyclophosphamide. His post-treatment course was complicated by pancytopenia, grade 1 cytokine release syndrome and grade 1 neurotoxicity. A PET/CT 1 month after treatment showed CR. Bone marrow biopsy at 1 month showed no evidence of large B cell or lymphoplasmacytic lymphoma and B-cell aplasia was evident in both the bone marrow and in the peripheral blood. Both the PET/CT and a bone marrow biopsy were repeated 6 months and 12 months after treatment and continued to show CR (Figure 2(b,c)). His serum IgM levels have normalized and no serum monoclonal gammopathy can be detected by immunofixation. He remains in complete remission at 12 months follow up.

WM is considered incurable. In symptomatic patients, the current treatment paradigm involves the use of anti-CD20 antibodies alone or in various combinations with alkylating agents, proteasome inhibitors or BTK inhibitors [6]. Autologous stem cell transplantation is reserved for relapsed chemosensitive disease, though only 40% of patients remain progression free at 5 years after transplant [7]. Histological transformation of WM is uncommon, however it is associated with a more aggressive disease course. In a published cohort of approximately 1500 patients, the rate of transformation was 3.8% at 15 years [8]. The risk of transformation is higher in the small subset of patients without the MYD88 mutation [9]. In retrospective studies, the median survival from the time of transformation has ranged from 16 to 32 months [8,10]. Most transformed patients present with high-risk features such as non-germinal center B-cell phenotype, extranodal involvement, and IPI scores ≥3 [10]. First-line treatment of transformed WM is R-CHOP or similar anthracycline-containing chemotherapy, with approximately 60% of patients achieving an initial response. These responses are, however, not durable, with a median progression-free survival of 9 months [10]. Treatment with hematopoietic stem cell transplantation has not shown a survival benefit; however, the number of patients reported is too small to draw a definitive conclusion [8,10].

CD19-targeted CAR T cell therapies have proven extremely effective in treatment of large B cell lymphoma and have often led to durable response. In the pivotal ZUMA-1 and JULIET trials, patients with r/r large B cell lymphomas were treated with CD19 specific CAR-T cells.
The trials reported 30–40% of patients with a durable response beyond 1 year, and patients with high-risk genetic features such as MYC and BCL2 and/or BCL6 rearrangements had similar response rates to other subgroups. However, patients with transformed WM were not included in these studies and most ongoing CAR-T trials in indolent lymphoma do not include patients with WM.

This case shows that CAR-T cell therapy is effective in treatment of transformed WM and can eliminate the transformed component as well as the underlying indolent lymphoma. Longer term follow up in this patient will be informative, as late relapses have occurred even in patients who achieve a deep response after transplant [7]. CAR-T cell therapy may be an effective treatment for relapsed or refractory WM that has not yet undergone histological transformation, as CD19 is almost universally expressed on lymphoplasmacytic lymphoma cells. This should be evaluated in the context of clinical trials. We eagerly await the results of ongoing, early phase clinical trials with CAR T cell therapy that specifically include patients with WM [14].

Disclosure statement
No potential conflict of interest was reported by the authors.

References


