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Case Report

Successful CAR-T cell treatment of aggressive B-cell lymphoma associated with a myeloproliferative disorder treated with a JAK1/2 inhibitor

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Introduction

We have recently reported the association of diffuse large B-cell lymphomas following JAK1/2 inhibitor treatment in patients with myeloproliferative disorders (MPD). While this is a rare event, the outcome of these patients is rather poor. In the past years, CAR-T cell treatment has emerged as the standard of care in transplant eligible patients with relapsed or refractory DLBCL after at least one line of treatment [1,2]. Here we report successful treatment of a 47-year-old patient with axicabtagene ciloleucel [3], who developed a refractory DLBCL after being treated with ruxolitinib for 13 months due to his prior existing JAK2 positive myeloproliferative disorder.

Keywords: CAR-T cells; Aggressive B-cell lymphoma; Immunosuppression; JAK1/2 Inhibition; Myeloproliferative Disorders

Case Report

The patient was diagnosed with JAK2 positive essential thrombocythemia (ET) in 2009 at the age of 35. In accordance with current guidelines, treatment with hydroxyurea was initiated [4]. After two months, this treatment was replaced by PEGylated interferon-α (Pegasys®) in January 2010. Interferon was discontinued after 96 months due to development of severe drug-induced psoriasis (plaque psoriasis) and psoriatic arthritis (dactylitis), while the patient was in haematological response. For this reason, he was put on the JAK1/2 inhibitor ruxolitinib (2*10mg/d) in August 2019. In September 2020, 13 months after initiation of the JAK1/2 inhibitor treatment, the patient developed a persisting cough. This led to the diagnosis of a diffuse large B-cell lymphoma (mediastinal bulk and generalized lymphadenopathy) which was ultimately verified by a bone marrow biopsy. Here, diffuse infiltration of the cell rich bone marrow with 5% lymphoma infiltration was found (Figure 1a). The lymphoma was of anaplastic subtype and non-GCB by the algorithm of Hans. FISH analyses for MYC and BCL-2 was inconclusive, but the double expressor score by Green scored 2 with expression of myc and bcl-2. Immunohistochemistry was strongly positive for MUM1, CD19, CD20, CD79 and showed a pronounced reactivity for p53. Genetic analyses of p53 showed no genetic aberrations or anomalies. The clinical stage was IV showing an FDG-avid mediastinal bulk, pronounced FDG-avidity in multiple supra- and infradiaphragmal lymph nodes and the right pleura, as well as multiple osseous secondary blastomatous lesions. Involvement of the left kidney was also suspected at this time. International prognostic index (IPI) was 4. The JAK1/2 inhibitor was discontinued, and the patient was treated with 2 cycles of RR- EPOCH followed by one cycle of R-COMP. At interim staging the disease was in complete response (Deauville: 3). Treatment was continued with 3 additional cycles of R-COMP with addition of lenalidomide (10mg) and two final cycles of rituximab monotherapy. Because of the high-risk features of this lymphoma (immunosuppression associated, high IPI score and double expressor score of 2), the patient was deemed eligible for CAR-T cell treatment by the local tumour-board (consolidation in remission). After bridging therapy with rituximab + polatuzumab vedotin + bendamustine the patient received lymphodepletion with standard fludarabine + cyclophosphamide and was infused with axicabtagene ciloleucel on 22.11.2021 with 0,4-2x10^6 cells. CAR-T cell therapy was tolerated well with CRS Grade I treated early with two doses of tocilizumab and no neurotoxicity. The patient was discharged with standard prophylaxis (valaciclovir, trimethoprim). A bone marrow biopsy on day 93 showed no signs of lymphoma with minimal signs of MPD (Figure 1b). Despite predeceasing (JAK1/2 inhibition) and ongoing immunosuppression (CAR-T), the patient did not experience infectious complications. Neutropenia was treated with GCS-F until day 36. The patient is still in CR after one year. Circulating CAR-T cells were detected 4 months after infusion and the patient has no circulating B-cells with IgG levels of 520mg/dl at nadir. Late complications included leukopenia and a herpes simplex infection as well as a pneumonia. After 12 months the patient is still in complete response from his lymphoma and does not need treatment for his myeloproliferative disorder (WBC: 7,8 G/L, ANC: 5,46 G/L, ALC: 4,68 G/L, Hb: 13,2 mg/dl, Pl: 182 G/L). Platelet counts are still within the normal range (Figure 2). The JAK2 allelic burden in peripheral blood and bone marrow is shown in Figure 2.

Discussion

Aggressive B-cell lymphoma development in the context of JAK1/2 inhibitor treatment for MPN is a rare but serious complication with poor outcome [5]. In our initial series only 2 of 6 patients survived with conventional anti-lymphoma therapy. It has been debated whether B-cell lymphomas developing during JAK inhibitor therapy are caused by these drugs or occur during this type of treatment due to general immunosuppression or other reasons [6-8]. CAR-T cells are well established in the treatment of r/r DLBCL and have recently shown remarkable efficacy in immunosuppressed patients with PTLD (3853 ASH Meeting 2021 Liu et.al). Here we report the first case to our knowledge of successfully treated JAK inhibitor associated DLCBL with CAR-T cells. Our patient developed the DLBCL 13 months after initiation of ruxolitinib, which lies within the reported time range. In contrast to some of our previous cases, no predeceasing clonal immunoglobulin rearrangement (IgR) was found in the bone marrow. The patient received standard treatment with R-CHOP based therapy and responded. However, the lymphoma features indicated high risk (IPI 4, disseminated involvement of extra nodal sites) typical for this type of lymphoma. Therefore, we chose treatment with axicabtagene ciloleucel in this young patient [3]. This decision was also made because of our previous experience with similar patients. Of note, CAR-T cells were given while the patient was in complete remission. This has previously been shown to be associated with excellent outcome in DLBCL [9]. CAR-T cells were well tolerated with few infectious complications. The patient had received ruxolitinib as third line treatment for his ET. The histological signs of ET, as well as the JAK2 burden diminished during treatment with this drug (Figure 2a and 2b). After the development of the lymphoma, ruxolitinib was stopped. Nevertheless, the MPD is currently controlled without treatment and stable despite discontinuation of ruxolitinib and CAR-T cell treatment. The patient was managed with infectious prophylaxis and is back to work.

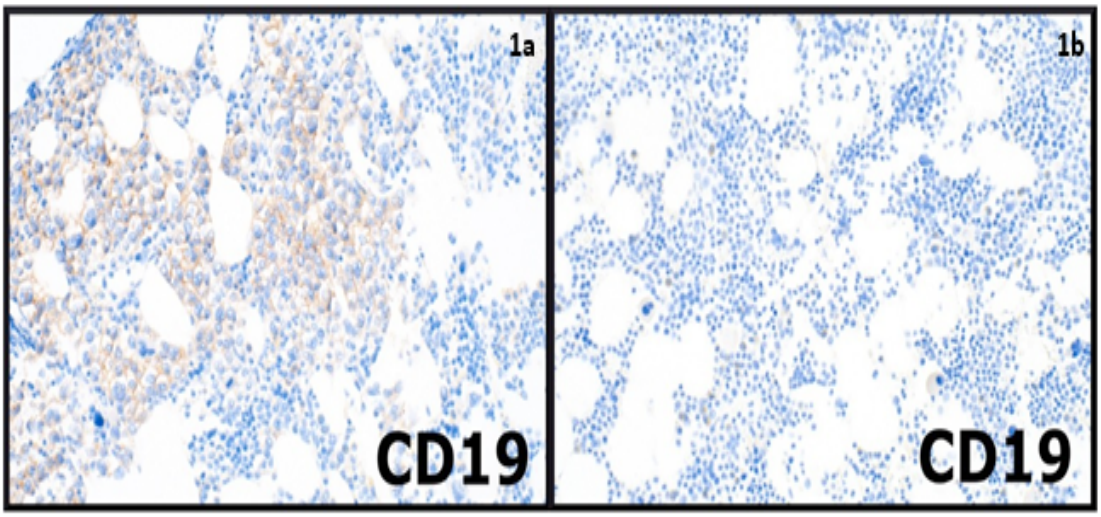
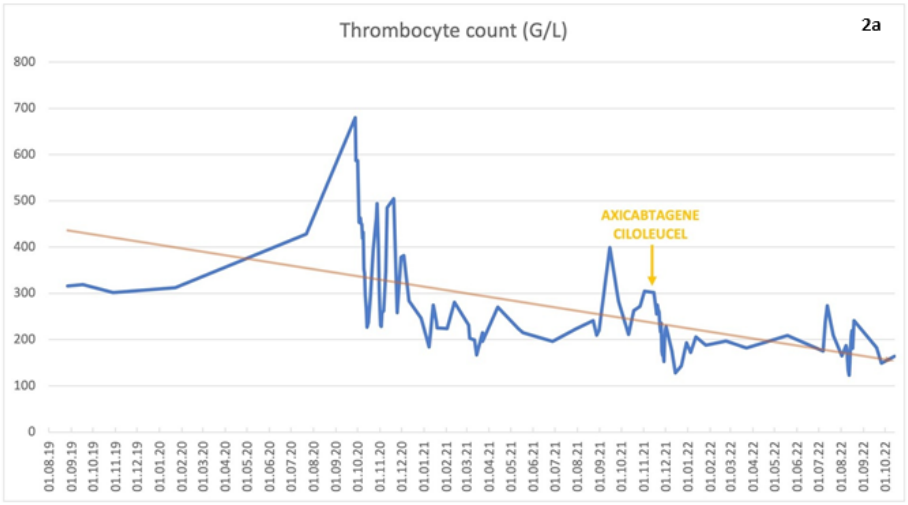


Figure 1a and 1b: 1a. Diffuse lymphoma infiltration of 5% in the bone marrow; 1b. Bone marrow biopsy 93 days after CAR-T cell infusion showing no signs of lymphoma and minimal signs of MDS.



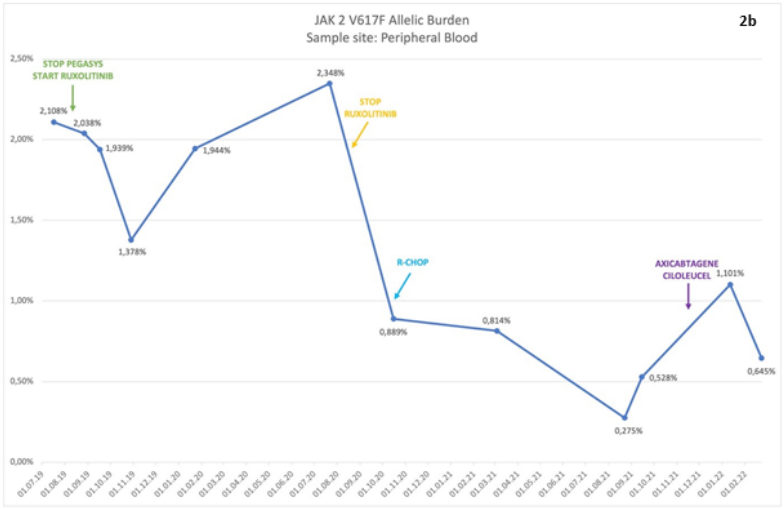


Figure 2a and b: 2a Platelet count during the course of disease; 2b JAK2 allelic burden in the peripheral blood.

Clinical Practice Points

This case shows the feasibility and efficacy of CAR-T cell treatment in patients with aggressive B-cell lymphoma developing under JAK1/2 inhibitor therapy. This may become more important with increasing numbers of patients being treated with JAK inhibitors for hematologic, rheumatologic and dermatologic disorders, as well as malignant and autoimmune diseases, regardless whether the lymphoma is directly associated with JAK1/2 inhibition or simply develops under treatment with this drug class [10,11].

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Significance: CAR-T cell therapy of JAK1/2 inhibitor associated aggressive B-Cell lymphoma is feasible and results in durable remissions with acceptable toxicity.

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