High-dose intravenous immunoglobulin may be an efficient treatment option for patients with late-onset high-grade immune effector cell-associated hematotoxicity refractory to standard therapies

Chimeric antigen receptor T-cell (CAR T) therapy has emerged as a transformative treatment for relapsed or refractory large B-cell lymphoma (LBCL), offering significant remission rates in patients who previously had limited therapeutic options.[1] However, this therapy is associated with a variety of toxicities, with immune effector cell-associated hematotoxicity (ICAHT) being recently identified as one of the most prevalent among these adverse events.[2] ICAHT is characterized by bone marrow (BM) dysfunction and secondary cytopenias, which puts such patients at high risk of infections.[3] The cornerstone of treatment for these toxicities is supportive care, including blood and/or platelet transfusions, when necessary, the administration of growth factors such as granulocyte-colony stimulating factor (G-CSF) and thrombopoietin (TPO) agonists and autologous CD34 stem cell boost, when available.[2] Yet, around 20% of patients fail to respond to supportive care, and thus face prolonged periods of a significantly increased risk of life-threatening complications, in particular infections.[3] Therapeutic options for these individuals are limited, and some of them will ultimately require allogeneic stem cell transplantation as the only treatment modality allowing to restore their BM function. However, given the substantial morbidity and mortality associated with this procedure, particularly for such a vulnerable patient population, this option has to be very carefully considered in each case. Hence, there is a need for novel therapeutic strategies for patients with ICAHT refractory to growth factors. Over the last decades, high-dose intravenous immunoglobulin (IVIG) has been used to manage BM toxicities associated with various autoimmune and inflammatory diseases. IVIG may act through the modulation of main components of the innate and adaptive immune system, such as pathogenic auto-antibodies, dendritic cells, neutrophils and T-regulatory cells.[4-8] We have therefore hypothesized that this option might be effective in the treatment of refractory ICAHT and present herein two cases of successful utilization of high-dose IVIG in patients with late grade 4 ICAHT following CAR T-cell therapy.

All the procedures involved in this study were in accordance with the ethical standards of the Institutional Review Board of the Rambam Health Care Campus (approval ##0673-19-RMB) and with the 1964 Declaration of Helsinki and its later amendments. The participants signed the informed consent form.

Case 1

A 75-year-old woman with a history of hypertension and type 2 diabetes mellitus was diagnosed 8 years prior to her current presentation with low-grade nodal marginal zone lymphoma. As she was asymptomatic, the "watchful waiting" approach was chosen. Five years later, the disease transformed into LBCL, and she achieved complete remission (CR) following therapy with rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate), and prednisone (R-CHOP). After a subsequent relapse, the patient was treated with polatuzumab vedotin combined with gemcitabine, oxaliplatin, and rituximab (GEMOX-R), achieving CR. Six months prior to her current presentation, she developed fatigue and shortness of breath. Laboratory tests showed worsening pancytopenia, and positron emission tomography/computed tomography (PET/CT) revealed extensive nodular disease with BM involvement, indicating yet another recurrence. Therefore, the patient was scheduled for CAR T-cell therapy for refractory LBCL. After lymphodepletion with fludarabine and cyclophosphamide, CAR T-cell therapy (axicabtagene ciloleucel) was infused. On day +7 post-infusion, she developed grade 1 cytokine release syndrome (CRS), and a single dose of tocilizumab was administered, leading to fever resolution by the following day. During that period, her complete blood count (CBC) declined, but at discharge, all values, except the platelet count, returned to baseline, with a white blood cell (WBC) count of $2.0x10^3/\mu L$, a neutrophil count of $1.55x10^3/\mu L$, a hemoglobin level of 8.3 g/dL, and a platelet count of $30x10^3/\mu L$ (baseline $80x10^3/\mu L$).

On day +25, the patient presented with septic shock and secondary acute respiratory distress syndrome, necessitating mechanical ventilation and norepinephrine support. Her WBC count was severely decreased at $0.2x10^3/\mu L$, with no detectable neutrophils. The platelet count was $8x10^3/\mu L$ and the immunoglobulin G level was 420 mg/dL. Extended-spectrum β-lactamase-producing *E. coli* bacteremia was identified, and the central line catheter was removed. Urine cultures were negative, and an abdominal CT scan revealed no infectious source. Meropenem was initiated, along with G-CSF and eltrombopag as supportive treatments. The fever resolved, and she stabilized, allowing for extubation 2 weeks later. However, her CBC remained persistently low in the weeks that followed, despite escalating doses of G-CSF and eltrombopag. A comprehensive workup was performed, which ruled out any infectious causes, including bacterial or fungal infections. Serum polymerase chain

reaction (PCR) tests for cytomegalovirus and Epstein-Barr virus were negative, with the serology indicating past infections. Parvovirus testing was also negative, and the vitamin profile was within the normal range. A thorough review of her medications identified no potential culprits. CRS was considered unlikely due to the absence of relevant symptoms.[9] Ferritin levels ranged between 1,000-3,000 ng/mL, possibly attributable to the recent septic episode, but normal triglyceride levels along with the lack of other criteria for hemophagocytic lymphohistiocytosis such as fever, splenomegaly or hemophagocytic cells in the BM made this diagnosis unlikely. Anti-neutrophil antibodies were assessed using the granulocyte immunofluorescence test (GIFT) assay with flow cytometry.[10] The results were positive for all the four HNA-typed donors, with the mean fluorescence intensity (MFI) being 5-fold higher than that of the negative control. BM examination revealed aplastic marrow with no signs of dysplasia or malignant cell infiltrates. Flow cytometry of peripheral blood showed no evidence of large granular cells. Furthermore, 8% of CAR T cells were identified in the BM. Therefore, late ICAHT grade 4 was considered to be the most likely diagnosis. Despite doses of G-CSF up to 480 mcg/day and eltrombopag up to 150 mg/day, her cell counts did not improve, and growth factors were discontinued 4 weeks after their initiation. Stem cell transplantation was considered, but ultimately rejected, given the high risk of mortality associated with her age and overall health condition.

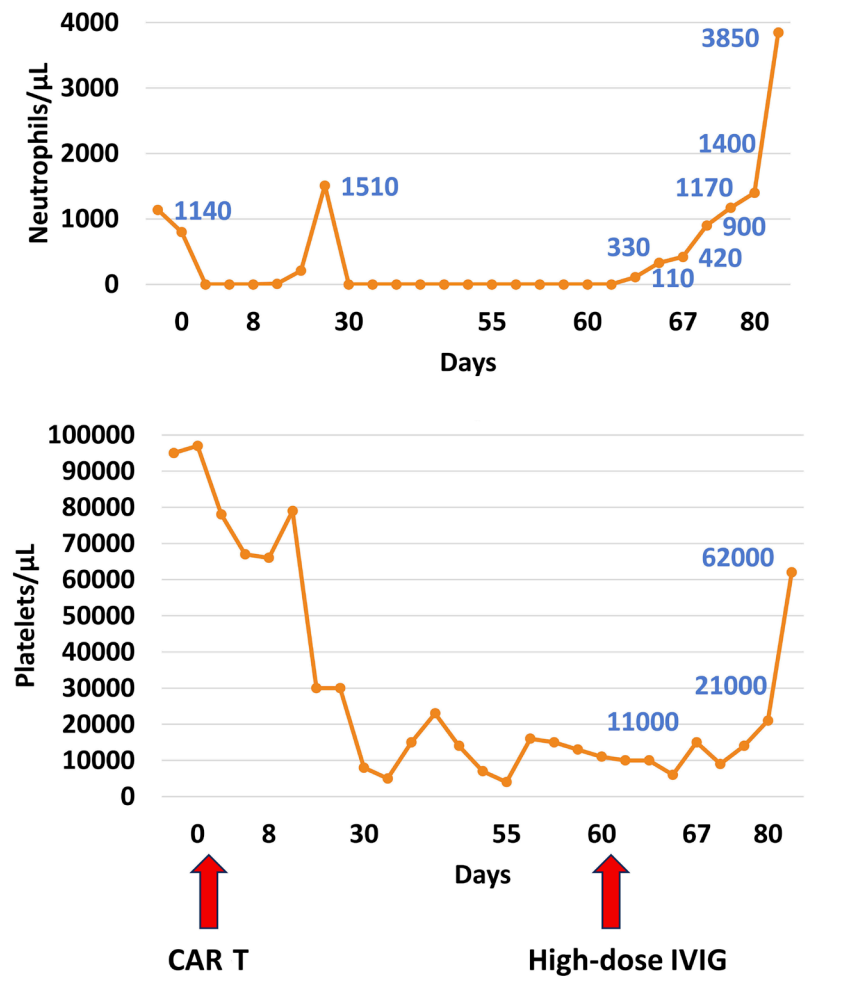

Figure 1. Dynamics of neutrophil and platelet counts in patient 1. CAR T: chimeric antigen receptor T-cell therapy; IVIG: intravenous immunoglobulin.

Two months (day +60) after CAR T-cell therapy initiation and approximately 1 month after the latest admission, cell counts were still low. Following a thorough case review the multidisciplinary team decided to administer a course of high-dose IVIG (2 g/kg), to be given in divided doses (0.5 g/kg/day) over 4 consecutive days. By the end of the first week of this treatment, cell counts started to gradually increase, and by day +80, the neutrophil count reached a value of around 1.4x10^3/µL for the first time within 2 months (Figure 1). Then, she was discharged with a WBC count of 2.0x10^3/µL, a platelet count of 30x10^3/µL, and a hemoglobin level of 8.3 g/dL. Importantly, the PET/CT revealed complete response of LBCL. At the most recent follow-up (day +130), the WBC count was within the normal range, and hemoglobin (10.2 g/dL) and platelet counts (62x10^3/µL) returned to the range of her baseline values.

Case 2

A 41-year-old man, otherwise healthy, was diagnosed with stage IVB, grade 3b follicular lymphoma. He was initially treated with three courses of obinutuzumab combined with CHOP, followed by two courses of obinutuzumab combined with dexamethasone, high-dose cytarabine (Ara-C) and cisplatin (Platinol), but failed to achieve an adequate response. Subsequently, axicabtagene ciloleucel was administered. PET/CT scans performed at 1, 3, and 12 months post-treatment demonstrated complete resolution of the disease. However, after CAR T-cell administration, the patient developed prolonged grade 4 neutropenia (CTCAE) that had not resolved after 30 months despite multiple courses of G-CSF injections. His platelet and hemoglobin counts were within the normal range.

An extensive evaluation, conducted to determine the cause of the prolonged neutropenia, included investigations of causes of infection (both bacterial and viral), nutritional deficiencies (B12 and folic acid), multiple BM examinations, and flow cytometry to rule out T-cell large granular lymphocyte leukemia. All findings were negative, and late grade 3-4 ICAHT was considered the most likely diagnosis. Levels of anti-neutrophil antibodies were mildly positive. Based on the promising outcome of the previous patient, high-dose IVIG (2 g/kg) was initiated in four divided doses. One week later, his neutrophil count substantially improved (2.8-3.2x10^3/µL) and remained normal over the following month (Figure 2).

The precise mechanism of ICAHT is not entirely clear, but it is suggested to involve cytokine secretion and an inflammatory response, resulting in BM dysfunction.[3] Based on this, a risk stratification tool known as CAR-HEMATOTOX, which evaluates both baseline hyperinflammation and impaired hematopoietic reserve, is now used before lymphodepletion to assess patient' ICAHT risk. The collection of autologous stem cells before CAR T-cell therapy administration, especially for patients with a high CAR-HEMATOTOX score, should be considered on an individual case basis.

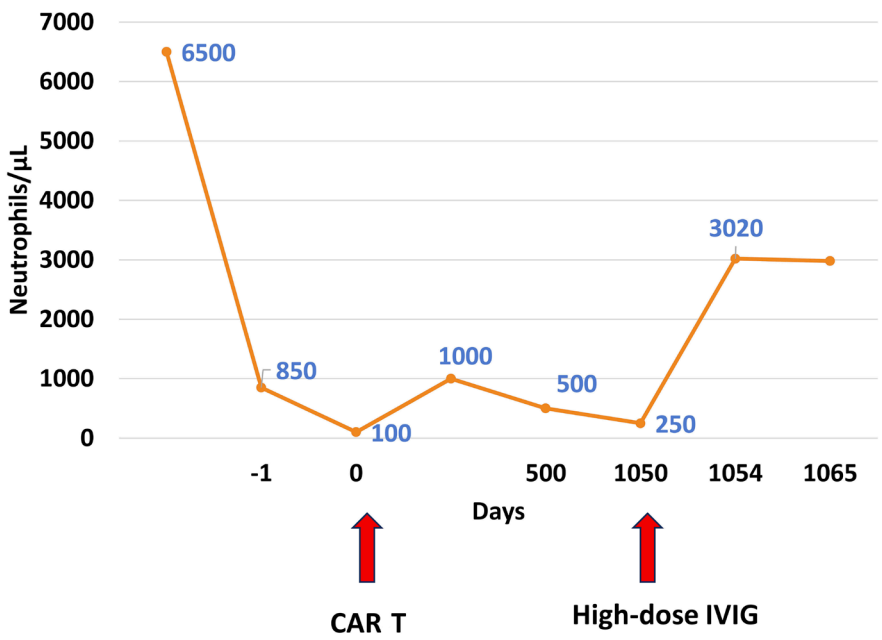

Figure 2. Dynamics of neutrophil counts in patient 2. CAR T: chimeric antigen receptor T-cell therapy; IVIG: intravenous immunoglobulin.

The initial treatment of this toxicity is generally supportive.[2] Low-dose corticosteroid therapy has been proposed and may be offered to patients unresponsive to G-CSF.[11] However, the management of patients with refractory, severe, and life-threatening ICAHT presents a unique challenge. Currently, in cases where anti-inflammatory agents and growth factors prove inefficient, and no autologous CD34 cells are available, allogeneic stem cell transplantation remains the only potential curative option. Yet, its association with significant morbidity and mortality and the unavoidable CAR T-cell eradication[3] markedly restrict its utility in this context. Hence, the identification of alternative treatment modalities is warranted. Given that high-dose IVIG is a safe and routine treatment for various autoimmune and inflammatory diseases affecting the BM, primarily antibody-mediated cytopenias, this therapy has been tried in patients reported herein, particularly in view of its limited toxicity. In both cases, after periods of prolonged refractory cytopenia, following IVIG administration, cell counts started to improve, with a faster and more substantial response in the second patient. A potential mechanism for the observed response may involve the inhibitory effect of IVIG on T-cell proliferation, which has been shown to occur in a dose-dependent manner.[12] Additionally, IVIG may contain antibodies that target various immunologically relevant molecules, such as interleukin-6 and tumor necrosis factor-α.[13,14] It may also help clear autoantibodies against neutrophils or platelets, akin to the mechanism seen in immune thrombocytopenic purpura, thus contributing to its therapeutic effects.[15] Obviously, despite the temporal association, these findings support but do not prove a causal relationship between the administration of IVIG and the improvement in cell counts, since ICAHT can occasionally resolve spontaneously.

The presented cases suggest that high-dose IVIG may be a potential treatment option for patients with refractory ICAHT who do not respond to conventional supportive therapies, such as G-CSF and TPO agonists. Given the observed promising results and the acceptable safety profile of IVIG compared to the risks associated with severe ICAHT, further investigation could be beneficial to assess the effectiveness of high-dose IVIG for this challenging clinical condition.

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Contributions

YL collected the data, analyzed and interpreted the data and wrote the paper. SR-H, DK, RF, Dy-O, LB, NS-M, EB IG and TZ collected and analyzed the data. OB-K conceived and designed the study, supervised the study, interpreted the data and wrote the paper. All authors contributed to writing and/or editing of the manuscript and approved the final version of the paper.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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