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# Tisagenlecleucel CAR-T for relapsed/refractory diffuse large B-cell lymphoma; one therapy, two clinical presentations: urgent need to design adverse event predictors

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Chimeric antigen receptor (CAR) T-cell therapy for diffuse large B-cell lymphoma (DLBCL) has revolutionized treatment outcomes yet it poses new challenges to clinicians. In parallel with its success, CAR-T will inevitably reach clinical units inexperienced in the use of this treatment type.

That was the case in Poland, where the Ministry of Health launched a reimbursement of tisagenlecleucel for adult patients with CD19-positive lymphoid malignancies only in 2022 [1]. In this article, we aim to compare the first two cases of patients treated with tisagenlecleucel at the Department of Hematology, Transplantation and Internal Medicine in the Medical University of Warsaw, Poland. The two patients developed highly contrasting clinical presentations after CAR-T infusion. The different clinical courses between these subjects constitute a valuable example of the highly variable systemic responses to tisagenlecleucel. In addition, we briefly discuss an adverse event (AE) prediction concept developed by research teams worldwide.

Initially, both patients were diagnosed with DLBCL not otherwise specified (NOS) and were subsequently treated in units not certified for CAR-T. A summary of the patients' treatment before CAR-T is set out in Table I. Initially, Patient#1 had a stage IV DLBCL compared to a stage II E diagnosed in Patient#2 [2]. Both patients were females with no comorbidities except for obesity in Patient#1. Moreover, both had no bone marrow or central nervous system (CNS) involvement at the time of diagnosis. Their detailed characteristics are given in Table I. Notably, at the time of diagnosis, Patient#2 was in the 24$^{th}$ week of pregnancy.

Following the diagnosis, Patient#1 received six cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone) chemoimmunotherapy with subsequent irradiation of the involved areas (IF-RT). Due to progressive disease, the patient received R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) salvage therapy. Additionally, MTX/DEX (methotrexate, dexamethasone) was administered intrathecally for CNS prophylaxis. After one cycle of R-DHAP, the treatment was continued with R-ICE (rituximab, ifosfamide, carboplatin, etoposide) due to a lack of response to the former (disease progression, macroscopic assessment). Subsequently, the patient was qualified for CAR-T and continued R-ICE as a bridging therapy, resulting in remission prior to CAR-T treatment.

On the other hand, Patient#2 received pre-phase treatment with cyclophosphamide and glucocorticoids followed by four cycles of CHOP, four cycles of R-CHOP, and IF-RT. Subsequently, four cycles of R-ICE were administered, resulting in progressive disease and Patient#2 was qualified for CAR-T therapy. Later, due to the large tumor burden, the intention-to-treat was to administer Pola-BR (polatuzumab vedotin, bendamustine, rituximab) as bridging therapy before CAR-T. However, because of progression the patient subsequently received one cycle of R-DHAP, with macroscopic progression during the cycle, and one cycle of GemOX (gemcitabine and oxaliplatin), administered because of a coronavirus disease 2019 (COVID-19) diagnosis at the planned time of the initiation of lymphodepleting chemotherapy. R-DHAP was complicated by sepsis caused by *Klebsiella pneumoniae*. Moreover, thrombosis of the

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**Table I.** Clinical course of patients — general characteristics

| | Patient#1 | | Patient#2 | |
|---|---|---|---|---|
| | | Date* | | Date* |
| Sex, age | Female, 45 | N/A | Female, 38 | N/A |
| Diagnosis (IHC confirmed) | DLBCL, NOS, non-GCB, MYC-positive, BCL2-positive<br>Ki-67 95% | Apr 2021 | DLBCL, NOS, GCB, MYC-negative BCL2-negative<br>Ki-6 100%<br>mut*TP53*-positive | Jun 2021 |
| Disease stage at diagnosis (Lugano classification) | IV | Apr 2021 | II E | Jun 2021 |
| Prephase treatment | – | – | CTX + GCs | Jun 2021 |
| First-line therapy | R-CHOP (6 cycles) | 2021 | CHOP (4 cycles)<br>R-CHOP (4 cycles) | Jul–Nov 2021 |
| | IF-RT | 2021 | – | ----- |
| Salvage therapy | R-DHAP (1 cycle) | May 2022 | IF-RT (50 Gy – 2 Gy × 25 fractions) | Dec 2021–Jan 2022 |
| Second-line salvage therapy | R-ICE (1 cycle) | Jun 2022 | R-ICE (4 cycles) | May–Aug 2022 |
| Bridging therapy | R-ICE (2 cycles) | Jul–Aug 2022 | P + BR<br>R-DHAP (1 cycle)<br>GemOX (1 cycle) | Sep 2022<br>Oct 2022<br>Nov 2022 |
| Other therapeutic regimens | Intrathecal MTX/DEX | May 2022 | mPRED 96mg/day | Aug 2022 |
| Disease status at lymphodepletion | CR | | PD | |
| Lymphodepletion | Flu/CTX | Sep 2022 | Flu/CTX | Nov 2022 |
| CAR-T infusion | Completed | Sep 2022 | Completed | Nov 2022 |
| Treatment result | CR | Dec 2022 | PD | Dec 2022 |
| CRS | No | – | Grade 3 | Nov 2022 |
| CRS characteristics | N/A | N/A | Fever >40°C<br>BP 90/60, peripheral hypoperfusion, HR 150, facial and neck edema, elevated CRP and IL-6<br>ICU admission: oxygen delivery 25 l/min, vasopressor, tocilizumab administration | N/A |
| ICANS | No | – | Grade 1 | Nov–Dec 2022 |
| ICANS characteristics | N/A | N/A | ICE score 8, confusional state, mental status changes | N/A |
| EASIX score before lymphodepletion | 0.88 | Sep 2022 | 1.50 | Nov 2022 |
| EASIX score on infusion day | 0.95 | Sep 2022 | 1.08 | Nov 2022 |
| EASIX-F score before lymphodepletion | 183.54 | Sep 2022 | 682.52 | Nov 2022 |
| EASIX-F score on infusion day | 149.72 | Sep 2022 | 887.37 | Nov 2022 |

*Date of observation/procedure/treatment duration; ABC — activated B-cell; BCL2 — B-cell lymphoma 2 protein; BP — blood pressure; CAR-T — chimeric antigen receptor T-cells; CR — complete remission; CRP — C-reactive protein; CRS — cytokine release syndrome; CTX — cyclophosphamide; DLBCL — diffuse large B-cell lymphoma; EASIX — Endothelial Activation and Stress Index, defined as [lactate dehydrogenase (LDH); U/L] × creatinine [mg/dL])/platelets [PLTs; × $10^9$/L]; EASIX-F — defined as EASIX × ferritin [ng/mL]; Flu/CTX — fludarabine + cyclophosphamide; GCs — glucocorticoids; GCB — germinal B-center; GemOX — gemcitabine + oxaliplatin; Gy — gray; HR — heart rate; ICANS — immune effector cell-associated neurotoxicity syndrome; ICE — immune effector cell encephalopathy; ICU — intensive care unit; IF-RT — involved-field radiation therapy; IHC — immunohistochemistry; IL-6 — interleukin 6; Ki-67 — nuclear protein Ki-67; mPRED — methylprednisolone; MTX/DEX — methotrexate + dexamethasone; MYC — MYC proto-oncogene bHLH transcription factor; N/A — not applicable; NOS — not otherwise specified; P+BR — polatuzumab, vedotin + bendamustine, rituximab; PD — progressive disease; R-CHOP — rituximab + cyclophosphamide, adriamycin, vincristine, prednisone; R-DHAP — rituximab + dexamethasone, cytarabine, platinum agent; R-ICE — rituximab + ifosfamide, carboplatin, etoposide; TP53 — tumor protein P53

right iliac vein was diagnosed one day before the lymphodepletion, as well as acute pancreatitis in the course of lymphoma, infiltrating the pancreas.

In both cases, tisagenlecleucel was administered as initially planned. Following the infusion, Patient#1 experienced no AEs, whereas Patient#2 developed grade 3 cytokine release syndrome (CRS) and grade 1 neurotoxicity [immune effector cell-associated neurotoxicity syndrome (ICANS)] [3]. The onset of CRS was on day +1 post-infusion and manifested initially with increasing fever and facial edema. The patient's condition deteriorated, resulting in a transfer to the intensive care unit (ICU). The patient developed tachycardia, hypotension, fever, head and neck edema, and required oxygen therapy (details in Table I). Tocilizumab and vasopressors were administered, resulting in CRS subsiding on day +5 and a return from ICU. On day +6, the patient developed mild neurotoxicity symptoms (grade 1).

These two cases show very different clinical presentations following treatment, which could not be determined in advance. The current guidelines state that CRS prediction is not yet possible, indicating factors such as high tumor burden associated with a higher risk of CRS [3]. Recently, CRS and ICANS have been linked to endothelial dysfunction [4], and various endothelial activation markers have been proposed as AE predictors [5, 6]. The simplest measure of endothelial activation is the Endothelial Activation and Stress Index (EASIX), defined as [lactate dehydrogenase (LDH); U/L] × creatinine [mg/dL])/platelets [PLTs; × $10^9$/L] and its derivatives, for instance: EASIX × ferritin [4, 5]. The EASIX scores for Patients#1 and 2 are provided at the bottom of Table I, and have been calculated for day –7 (i.e. before lymphodepletion) and day 0 (day of CAR-T infusion). Unfortunately, EASIX scores are bias-susceptible. For instance, renal insufficiency or tumor lysis syndrome will lead to changes in creatinine and LDH concentrations, respectively, impacting EASIX.

Nevertheless, Penack et al. [4] have shown that a baseline EASIX of 4.67 could be used as a cutoff for severe CRS prediction (grade ≥3). And according to Pennisi et al. [7], EASIX scores before lymphodepletion are associated with CRS occurrence. The median value was 1.88 in Pennisi et al.'s 'CRS group' [7] compared to 1.06 in their 'no CRS group'.

Even so, EASIX scores are not validated predictors of CRS occurrence, and we cannot draw conclusions from the calculated values. However, as the endothelium can be damaged by factors such as chemotherapy, cytokines, or sepsis [8], it appears reasonable to deduce that Patient#2 developed AEs due to having been previously exposed to infection and more chemotherapy regimens. In addition, other factors predicting CRS are currently under investigation. When endothelial activation occurs, cytokines, adhesion molecules, and other markers such as angiopoietins, are released, and their serum concentrations are being evaluated as potentially more accurate predictors [6, 9].

To sum up, treating DLBCL with tisagenlecleucel may be associated with very different clinical scenarios that pose significant challenges for clinical teams. Therefore, accurate predictors of adverse events would be extremely beneficial, and endothelial activation is emerging as a potential candidate.

## Authors' contributions

All authors contributed equally to manuscript preparation. All authors read and agreed to published version of manuscript.

## Conflict of interest

The authors declare no conflict of interest.

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## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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