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CAR T-cell therapy in diffuse large B-cell lymphoma

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Summary Diffuse large B-cell lymphoma (DLBCL) comprises 30–40% of non-Hodgkin's lymphoma. Clinical factors such as a high International Prognostic Index (IPI) or molecular factors as cell of origin (COO) have an influence on the clinical outcome after conventional immunochemotherapy. Patients with resistant or relapsed (r/r) DLBCL have a poor prognosis with a median overall survival of 6,3 months and low complete response rates (CR 7%) to salvage chemoimmunotherapy. Currently, therapy with autologous chimeric antigen receptor T-cells (CAR T-cells) provide encouraging complete responses (CR) of up to 50%. However, high costs for approved products and elaborate logistics have to be encountered.

Keywords Tisagenlecleucel · Axicabtagene ciloleucel · Cytokine Release Syndrome · Autologous chimeric antigen receptor T-cells · Diffuse large B-cell lymphoma

Introduction

With standard immunochemotherapy, e.g., R-CHOP (rituximab+ cyclophosphamide, doxorubicin, vincristine, and prednisone), patients with diffuse large B-cell lymphoma (DLBCL) can achieve an overall response rate (ORR) of 60% resulting in a long-term event-free survival of 50% [1].

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Unfortunately, 30–40% of patients eventually relapse and 10% are primary refractory. Despite intensive salvage immunochemotherapy and autologous stem cell transplantation (ASCT), outcome in these patients is poor with an ORR of 27–63% and long-term survival in up to 48% [2]. With the introduction of (mostly autologous) chimeric antigen receptor T-cell (CAR-T) therapy, very encouraging results with CR rates up to 50% in r/r DLBCL have been demonstrated leading to approval of two products by the US FDA (Food and Drug Administration) and EMA (European Medicines Agency).

Chimeric antigen receptor T-cells

A CAR is commonly composed of a specificity-conferring extracellular antibody single chain variable fragment (scFv), a hinge region transmembrane domain, one or more intracellular costimulatory domains (e.g., CD28 or 4-1BB [CD137]), and a T-cell receptor signaling domain (CD3 ζ). Several generations of CARs can be distinguished, differing by co-stimulating signaling domains (CD28, 4–1 BB) being responsible for T-cell activation and expansion [3].

Approved CAR T-cells in hematological disease

At present two CAR-T products against CD19 are approved:

- Axicabtagen–ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
- Tisagenlecleucel (Kymriah®) for the treatment of pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse posttransplant or in

second or later relapse and adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

CAR T-cells in non-Hodgkin's lymphoma

With the introduction of CAR T-cells targeting CD19-positive lymphoid malignancies, encouraging response rates have been observed in heavily pretreated patients.

The ZUMA1 trial (NCT02348216) was the pivotal trial for axicabtagene ciloleucel incorporating a CD28 costimulatory domain (Axi-cel; Yescarta®). The trial included two cohorts with r/r lymphoma: cohort 1 which included 77 patients with r/r DLBCL and cohort 2 which included 24 patients with primarily mediastinal B-cell lymphoma (PMBCL) or transformed follicular NHL (tFL). After lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day (FC 30/500) for 3 days, 91% patients received a target dose of 2.0×10^6 CAR T-cells/kg body weight. Patients had median of 3 pretreatments (range 1–7), including autologous stem cell transplantation (ASCT) in 21%. Bridging therapy between enrollment in the study and lymphodepleting chemotherapy was not allowed. Observed specific toxicity was a cytokine release syndrome (CRS) in 93% (grade ≥3: 13%) and neurological toxicity (NT) in 64% (grade ≥3: 28%). More recently, an up-date with median follow-up of 15.4 months was published, confirming durable ORR of 83% and a CR of 58%. The COO had no impact on clinical outcome. Median duration of response was 11.1 months (4.2–not estimable), OS was not reached, progression-free survival (PFS) was 5.9 months (95% confidence interval [CI] 3.3–15.0). [4]. Furthermore, analysis of "real-world data" from different centers utilizing the approved, commercial available product, confirmed high activity in r/r DLBCL treated outside of clinical trial, while 50% of the patients did not meet inclusion criteria for different comorbidities [5, 6]. Despite higher comorbidity, slightly higher median age and higher proportion of patients receiving Axi-cel after relapse ASCT (27% and 33 % for "real-world data" compared to 23% in the ZUMA1 trial), the ORR was similar (71% and 81% for "real-world data" and 83% in the ZUMA1 trial) [6, 7].

Tisagenlecleucel (Tisa-cel) (Kymriah®), incorporating a 4-1BB costimulatory domain, was approved based on the JULIET trial (NCT02445248) for r/r DLBCL, including patients with a median of 3 prior therapies (range 1–8) including ASCT in 49%. After lymphodepleting chemotherapy with FC (25/250) or bendamustine 90 mg/m^2/day for 2 days, 93% of patients received a median single dose of 3.0×10^8 (range, $0.1–6.0 \times 10^8$) CAR-T cells. In 102/111 (92%) patients bridging therapy was given between leukocyte collection and CAR T-cell infusion. There was no treatment-related death observed. Best ORR was 52% (95% CI, 41–62) including 40% CR. Those patients that had obtained CR at 3 months were also more likely to remain in remission at 6 months after CAR-T infusion. Median duration of response was not reached at the time of analysis. For patients achieving a CR, the 12-month relapse-free survival rate was 79% with an OS of 95%. The OS probability at 12-months for all infused patients was 49% [8]. More recently, "real-word data" for tisagenlecleucel clearly support clinical activity with an ORR of 66% (CR 42%) [9].

A third CD19-directed CAR T-cell product, not yet approved, is currently investigated in the JCAR017-TRANSCEND trial (NCT02631044) using lisocabtagene maraleucel (Liso-cel) (incorporating a 4-1BB costimulatory domain). During manufacturing, T-cells are selected in CD4+ and CD8+ cells and then further processed to CAR-T separately. The product is prepared in two tubes consisting of CD4+ and CD8+ CAR-T cells in a precise 1:1 ratio. Patients were treated in two cohorts, including 73 patients DLBCL NOS and high grade B cell lymphoma and 102 patients with DLBCL NOS, PMBCL or tFL. Median of prior therapies was 3(range, 2–8, ASCT in 38%). A CRS occurred in 37% (grade ≥3: 1%) and NT in 23% (grade ≥3: 13%), the ORR was 80% including 55% CR [10]. Based on encouraging data, a submission to FDA for approval is expected next year. More recently, a subset of patients with secondary central nervous system (CNS) manifestation showed response in 4/9 patients cases [10, 11].

Assessment and management of adverse events in CAR T-cell therapy

CAR T-cell therapy is associated with significant acute toxicities, which can be severe or even fatal [12]. The following symptoms can be observed: cytokine release syndrome (CRS), neurotoxicity (CAR-T cell related encephalopathy syndrome [CRES] or immune effector cell associated neurotoxicity syndrome [iCANS]), cytopenia, prolonged B cell aplasia, hypo-gammaglobulinemia resulting in increased risk for infections and rarely hemophagocytic lymphohistiocytosis (HLH).

Cytokine release syndrome

Virtually all patients experience at least a mild cytokine release syndrome (CRS) presenting with fever >38.5 °C. The therapy of mild, i.e., grade I CRS, is symptomatic. Grade ≥2 CRS, which can include systolic blood pressure ≤90 mm Hg and/or hypoxia (FiO2 ≤40%) needs prompt interventions with IV fluids or non-invasive oxygen supply through breathing mask. If conditions deteriorate, CRS 3 is diagnosed and multiple pressor/resuscitator or respirator might become necessary; a CRS 4 means life-threating conditions. For monitoring of CRS proinflammatory parameters, e.g., CRP, ferritin or IL-6 can be used. As the time point of CRS may vary between day 1 to day 14 (me-

dian 5), patients will be observed in hospital for 14 days in most centers. As a side effect of lymphodepletion and CAR T infusion, B-cell aplasia and leukopenia can occur and therefore infection has to be ruled out in febrile patients, despite low incidence of infections during CAR T-cell therapy [13].

In moderate to severe symptoms, i.e., CRS ≥2 not responding to supportive therapy, tocilizumab, an interleukin-6 receptor antibody, is recommended. Tocilizumab inhibits direct binding of IL-6 or IL-6/soluble IL-6 receptor complex to cell membranes. Tocilizumab can be given at a dose of 8 mg/kg IV (max. 800 mg), every 8 h with a maximum of three doses within 24 h and a total of four doses. In case of CRS grade ≥3 or patients not responding to tocilizumab within 24 h, corticosteroids (methylprednisolone 1 g/kg or dexamethasone 10 mg twice daily) should be considered. So far, corticosteroids were not recommended as first-line for CRS due a possible interaction with T-cell expansion. However, a recently proposed regimen showed no negative impact on T-cell expansion [14]. Comparison of clinical data are difficult between trials, as different scoring systems and algorithms for CRS treatment were used. More recently, a simplified scoring system was introduced [15].

Immune effector cell associated neurotoxicity syndrome (iCANS)

Immune effector cell associated neurotoxicity syndrome (iCANS) is another major complication of CAR T-cell therapy which can occur with or independently of CRS, mostly within 28 days after CAR T-cell infusion. As CAR T-cells can cross the blood–brain barrier (BBB), endothelial cell activation might play a role in the development of iCANS and cerebral edema [16]. Clinical symptoms, e.g., diminished attention, confusion, word-finding difficulties, disorientation, aphasia, somnolence, seizures or cerebral edema may occur. Tocilizumab is not expected to cross the BBB and could theoretically increase the amount of circulating IL-6 in the brain. Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h is considered as rescue therapy of iCANS in patients without signs of CRS. In addition to seizure prophylaxis or treatment, brain imaging (CT-scan or MRI) should be considered to rule out cerebral edema. A vigilant observation and close monitoring using a neurological assessment score is strongly recommended.

B-cell aplasia

As off target toxicity B-cell aplasia can occur; therefore some patients are in need of immunoglobulin infusion in the case of recurrent infections or even prophylactically, depending to local guidelines.

Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome

Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS) rarely occurs and is characterized by similar clinical manifestations as CRS as high fever, multiorgan dysfunction or CNS disturbances.

Conclusion and perspective

CAR T-cell therapy is “en vogue” due to very promising response data in relapsed and refractory DLBCL and 50–70% of patients will be alive after 12 month trials. This has been confirmed in “real-world” data including patients not eligible for trials due to several comorbidities [5, 6, 9]. Despite the high efficacy of CAR T-cell therapy with CR rate up to 50%, which is in contrast to poor outcome after conventional salvage immune-chemotherapy, results have to be interpreted with caution [17]. So far, only data of single-arm phase II trials with highly selected patients and short observation times are available. Even “real-world” data do not really improve the information quality, as data were provided by only a few highly experienced centers. No randomized data comparing ASCT or allo-HSCT are available so far. Therefore, no recommendation can be given in patients relapsing or refractory to first line therapy if transplant eligible. Clinical trials comparing ASCT with CAR T-cell therapy are currently being initiated.

As CAR T-cell therapy is associated with specific toxicity as described above, has to be established a dedicated and well-trained team in specific centers. Finally, financial burden of CAR T-cell therapy is significant. Therefore, new funding systems are necessary. Furthermore, a significant proportion of patients are refractory to CAR-T cells. Pathomechims are only partially explained by a loss of the target structure (CD19) at the tumor cell or receptor mutations [18] or expression of checkpoint proteins by the tumor [19]. Administration of checkpoint inhibitors along with CAR-T cells are currently being tested: ZUMA-6 trial, axicabtagen-ciloleucel +anti-PD-L1 antibody atezolizumab or PORTIA trial using tisagenlecleucel +pembrolizumab. Combining different epitopes to improve activity of CAR T-cell therapy was recently applied in r/r leukemia providing CR of 73% in ALL using an anti-CD19/CD22 CAR-T [20].

Novel CAR-T constructs are directed against CD79b alone or in combination with CD19 in cell line- and patient-derived xenograft models and should be clinically tested in B-cell lymphoma [21]. A CD30 CAR T-cell therapy demonstrated activity in patients with Hodgkin lymphoma and anaplastic large cell lymphoma [22]. Ongoing concepts use CAR T-cell therapy in earlier lines, as randomized trials (ZUMA 7-NCT03391466; BELINDA-NCT03570892) compare CAR T-cell therapy versus ASCT in first relapse.

CAR-T cells have demonstrated significant clinical benefit in all studies published so far. Although Adverse Events (AEs) such as CRS, neurological toxicity, and B-cell aplasia are common, the majority of events are manageable when treated by an appropriately trained multidisciplinary team.

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