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Case Report

Allogeneic Chimeric Antigen Receptor T Cells: A Further Potential Weapon for Haematological Malignancies

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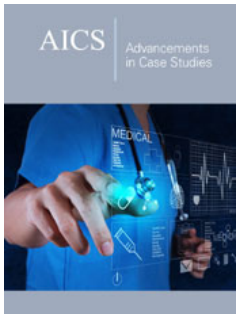

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Introduction

Autologous (patient-derived) Chimeric Antigen Receptor T (CAR T) cells have widely proven their efficacy to treat certain B-cell haematological malignancies [1-3]. However, autologous CAR-T presented some limitations regarding both the manufacturing process and the use of T cell exhaust due to several therapy lines [4,5]. The possibility to use cells from healthy donors, referred to as "off-the-shelf" allogeneic CAR T or universal CAR T (UCART) could potentially overcome these limitations, as well as making a marked reduction in costs due to the implementation of industrialized manufacturing process. At the same time, the creation of batches allowed the possibility to have a product immediately available also for redosing, if necessary. However, allogeneic approaches are associated with two major issues: the life-threatening Graft Versus Host Disease (GVHD) and the short persistence of allogeneic CAR-T due to host immune recognition. Here, we report the promising results of the main phase-1 clinical trials in haematological malignancies [6].

The Gene Editing Technology to Avoid GVHD and Host-Mediated Rejection

The use of donor-derived products potentially exposes patients to the risk of HLA mismatches which may lead to GVHD. Because αβ TCR is determinant of T cell alloreactivity, the gene edited technology has been used to prevent the expression of a functional TCR. To disrupt the gene encoding for TCR α-chain (TRAC), a technology based on the Transcription Activator-Like Effector Nuclease (TALEN®) was developed and validated [7,8]. TALEN are hybrid molecules of DNA recognition proteins linked to an endonuclease that can be engineered to cut specific sequences of DNA. All the clinical trials exposed below used the TALEN® platform (produced and controlled by Cellectis) to generate UCART. The success of gene editing approach to avoid GVHD led to applying the same technology to disrupt the gene of CD52. This allows administration of anti-CD52 antibody (ALLO-647) to suppress all CD52 positive immune cells that can mediate rejection such as T, B and NK cells, sparing UCART cells. All UCART clinical trials demonstrated the efficacy of this approach and included, in the lymphodepletion (LD) chemotherapy, the use of ALLO-647.

Clinical Application of Allo-Cart in Haematological Malignancies

UCART19 (anti-CD19) in pediatric and adult relapse/refractory (R/R) B-lineage acute lymphoblastic leukaemia (B-ALL) patients

Pall trial

The PALL trial evaluated the safety and anti-leukaemic activity of UCART19 in pediatric patients with R/R B-ALL. The study enrolled seven patients with a median age of 2.7 years (range 0.8-16.4). The median number of previous lines of therapy were 4 and 3 patients

received allo-SCT. All patients underwent LD with fludarabine (F) and cyclophosphamide (C) with or without alemtuzumab and received UCART19 at the fixed dose of 1.1–2.3 × 106 cells. The results showed 2 patients in remission at the time of publication, while 1 was refractory and 1 relapsed. Three deaths not treatment-related were observed: two for disease progression and 1 for viral infection. Among adverse events (AEs), the cytokine release syndrome (CRS) was the most common followed by neurotoxicity and acute skin GVHD. This study demonstrated for the first time the manageable safety profile of UCART19 in heavily pre-treated pediatric patients.

Calm trial

The CALM trial enrolled 25 adult patients with R/R B-ALL with a median age of 37 years (28-45) [9]. They received dose escalation of UCART19 (6x106, 6-8 x107, 1.8-2.4x108) after LD with FC with or without alemtuzumab. Three patients developed dose limiting toxicities (1 CRS grade 4 and 2 grade 4 prolonged cytopenia). 14 patients died, nine for progressive disease and five from infection or other complications. After a median follow-up of 12.8 months, the overall response rate (ORR) was 48%. Duration of response was 7.4 months, progression free survival (PFS) was 2.1 months and overall survival (OS) was 13.4 months. These results demonstrated that UCART19 is a valid option to treat adult patients with rapidly progressive all.

ALLO-501 (anti-CD19) in R/R (diffuse large B-cell lymphoma) DLBC and follicular lymphoma (FL)

Alpha study

ALPHA study evaluated the efficacy and the safety profile of escalating dose of ALLO-501 (40, 120 or 360 x 106) in adult patients with R/R DLBCL and FL [10]. 46 patients were enrolled, 37% (17/46) presented advanced stage after a median number of 4 prior lines. 20% of patients failed auto-CAR T. The safety resulted manageable with no DLT or GVHD. No grade ≥2 immune effector cell-associated neurotoxicity syndrome (ICANS) and limited CRS were observed. The infection rate was similar to that observed in autologous CAR-T. The 6-month complete remission (CR) rate resulted in 36.4% in DLBCL which was similar to the 6-month CR rates reported in the pivotal trials of autologous CAR T.

ALLO-501A (anti-CD19) in R/R FL and DLBC, transformed marginal zone lymphoma (tMZL) and primary

Alpha2

In this phase 1/2 trial, 15 heavily pretreated adult patients with different B-cells lymphoma subtypes (aggressive and indolent) were treated with ALLO-501A [11]. After LD they received single dose of ALLO-501A (40 [DL1] or 120 [DL2] x 106 viable CAR T cells) or consolidation dose of ALLO-501A (DL2). This study focused on the consolidation cohort (13 enrolled, 9 pts treated so far) in which no CRS, no GvHD, no ICANS, no DLTs were observed. Of the 12 evaluable patients, both ORR and CR were 50% while in the consolidation cohort, both ORR and CR rate were 66.7% with 3/3 partial response (PR) converted to CR after consolidation. These findings support the hypothesis that the consolidation dosing has comparable safety and an improved efficacy profile, compared to single dosing. Currently, an ALLO-501A phase-2 trial is ongoing.

UCART123v1.2 (anti-CD123) in R/R acute myeloid leukemia (AML)

The AMELI-01 trial experimented UCART123 in adult patients with R/R AML [12]. The end points of the study were the evaluation of safety, tolerability and expansion observed at escalating doses after FC with or without alemtuzumab. 18 patients with a median age of 57 years were enrolled. The median number of prior treatments was 4 and 50% of them underwent allo-SCT. The results showed that UCART123v1.2 expansion correlates with reduction in tumour burden at the dose of 6.25x105cells/kg although at the same dose UCART123 is not sufficient for sustained anti-leukemic activity and a second dose would then be given. The addition of alemtuzumab to FC regimen was associated with significantly higher UCART123 cell expansion which correlated with improved activity and cytokine profiles. Overall, the data supports further study of UCART123 with FCA 2-dose regimen.

ALLO-715 (anti-BCMA) in R/R MM

Universal study

The Universal study is the first allogeneic anti-BCMA CAR-T dose escalation trial in R/R MM [13]. The primary endpoints were the safety and efficacy of ALLO-715. 42 out of 47 patients enrolled were treated (5 progressed prior to treatment). Patients were heavily pretreated with a range of 3-11 lines of therapy. 19% presented ISS Stage III at screening, 34% had high risk cytogenetics and 19% had extramedullary disease. The most common grade (Gr) 3+ AEs included anemia, neutropenia, lymphopenia and thrombocytopenia. CRS occurred in 52.4%, all Gr 1/2 except 1 patient with Gr 3. Gr ≥3 infections occurred in 12.8% of patients, including 2 previously reported Gr 5 events (fungal pneumonia and adenovirus hepatitis). Early results from this trial have been presented at ASH 2020 and demonstrated that the higher dose level (DL) 3 and 4 (320 or 480 x 106 CAR-T cells) lead to clinically meaningful efficacy. Subsequent analysis regarding the subgroup who received the DL3 and DL4 (n=26) demonstrated that ORR was 61.5% and very good partial response or better (VGPR+) rate 38.5%. The median time to 1st response was 16 days. The median follow-up for the DL3/DL4 pts was 7.4 months with a median duration of response of 8.3 months. Of the 10 pts with a best response of VGPR+, 8 were found to be negative by minimal residual disease (MRD) analysis. ALLO-715 showed CAR-T cell dose response relationship with higher doses (DL3/DL4) leading to clinically meaningful efficacy. Indeed ALLO-715 presented a tolerable safety profile. FCA induces a deep and durable window of lymphocyte depletion allowing CAR-T cell expansion and persistence. A study using the next generation anti-BCMA CAR (ALLO-605) which supplies cytokine signaling to the CAR bearing cells is ongoing (IGNITE). The current Universal trial continues to enroll, including a cohort with consolidation, and updated data will be presented.

Conclusion

CAR-T cell therapy has changed the therapeutic landscape of some hematological malignancies and remains one of the most promising approaches in the treatment of cancer. The development of UCART cells therapy could overcome some autologous CAR-T limitations and significantly increase access to this class of immunotherapy. Gene editing technologies have already resulted in strategies to control the risk of GVHD by efficiently eliminating TCR expression and to make allogeneic CAR-T invisible to the host immune system. However, the major limitation of allogeneic CAR-T emerged following several clinical trials is the low persistence of the product itself. A consolidation booster may provide this limitation making up for persistence of UCART. In conclusion, the results of UCART clinical trials demonstrated the efficacy and safety of this innovative therapy also in patients heavily pre-treated included those who underwent allo or autologous SCT and/or submitted to autologous CAR-T.

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