Beyond Autologous CAR-Ts: Why is the New Wave of Cell Therapies in B-cell Lymphomas Inevitable?

The first wave of innovative cell therapies was indeed game-changing in the management of many hard-to-treat B-cell malignancies. The four key autologous CD19 targeting CAR-Ts i.e. Kymriah, Yescarta, Tecartus, and Breyanzi with various constructs, are currently approved across four heme malignancies – ALL, DLBCL, FL, and MCL. The current CAR-T approvals are primarily in heavily pretreated relapsed/refractory high unmet need late line settings and are moving to earlier lines.

Despite tremendous success, there are several limitations with autologous CAR-Ts that stymie their wider use and realization of their true potential. The major barriers are:

- Logistic challenges, lengthy manufacturing that delays therapy initiation
- Resistance to auto-CD19 CAR-T therapies; clonal escape or development of CD19-negative clones
- Health of T-cells from heavily pretreated patients
- High cost and resource utilization

Extensive clinical activity is ongoing to address these challenges. The new phase of promising cell therapies under development includes key new approaches such as *'off-the-shelf'* CD19 allogeneic CAR-Ts with nearly no vein-to-vein time, allogeneic CD19 CAR NK cells, exploration of alternative antigens beyond CD19, or dual bispecific antigen targeting CAR-Ts.

There were >80 CAR-T focused presentations at EHA and ASCO 2021 recently, showcasing novel approaches and data specifically in B-cell malignancies. Summarized below is the data from some of the key presentations.

Long vein-to-vein time, administrative and logistic challenges, low cell count, and poor viability are some of the key reasons that not only delay therapy initiation but also limit broader use of autologous CAR-Ts. The new CAR platforms such as allo-CAR-Ts can mitigate these issues but can additionally eliminate the need for apheresis and unnecessary bridging therapy while providing ready-to-use healthier T-cells and option for re-dosing with improved safety profile. These novel CAR approaches are also trying to address the unmet need of resistance to CAR-T therapy by cautiously studying post-CAR-T patients.

'Off-the-shelf' therapies such as allogenic CAR-Ts, dual targeting CAR-Ts, or NK cell therapy are eagerly awaited for the routine clinical use in near future. The key presentations at ASCO and EHA 2021 included:

Allogeneic CAR-Ts

ALLO 501 and ALLO 501A (CD19 targeting allo-CAR-T, TALEN gene editing): Allogene reported Phase I/II data for ALLO 501A in R/R NHL

- Phase I/II ALPHA2 study showed ORR of 56% and CR of 44% in patients who had not received previous CAR-T therapy. Safety was manageable, with absence of GvHD and neurotoxicity. There was one case of Gr3 CRS, while majority had only low-grade CRS. Rare Gr3 infections were seen (8%), which otherwise are common with the use of anti-CD52 for T-cell depletion.
- ALLO 501A can potentially work in patients exposed or refractory to rituximab, the mainstay treatment for most NHL patients.

PBCAR0191 (CD19 targeting allo-CAR-T): Precision Biosciences reported updated data from Phase I/IIa trial in R/R CD19+ NHL

- Impressively, median time from screening to treatment start reported is only 1 day, a major advantage over current autologous CAR-Ts.
- PBCAR0191 showed a high ORR of 89% and CR of 78% with a trend towards durable responses at ≥28 days in heavily pretreated patients who had 4+ prior lines of therapy. Mostly mild AEs were reported. There was an absence of Gr3 CRS, neurotoxicity, and GvHD, and only low Gr1/2 events were seen.
- The study also included patients with prior CAR-T therapy that is likely to help establish its use in CAR-T progressors.

CTX110 (CD19 targeting allo-CAR-T with CRISPR/Cas9 editing): CRISPR Therapeutics presented trial design of Phase I CARBON trial in R/R CD19+ DLBCL and subtypes

- Short time from screening to treatment compared to currently available autologous CAR-Ts.
- Early data suggested that CTX110 is active in R/R NHL with 100% ORR at the highest dose and CR showed trend towards durability at 3 months. Expected to have improved and manageable safety as the construct is designed to mitigate GvHD and rejection. Early data showed no GvHD or Gr3 CRS and neurotoxicity.

So far, allogeneic CAR-Ts have demonstrated comparable efficacy with a relatively better safety profile, that compares favorably with the currently approved autologous CAR-Ts, but with an advantage of ready availability facilitating minimal time from patient enrollment to treatment.

NK Cell Therapy

NK cells are actively being explored as an alternative ready-to-use novel CAR platform to address hurdles related to autologous CAR-Ts. Unlike T-cells, allogeneic NK cells do not cause GvHD and can be safely administered. The NK cells are naturally "off-the-shelf" and can be manufactured centrally so that the product is available on-demand. The preclinical and increasing early clinical data in lymphomas is promising.

NH019, an iPSCs-derived NK cell therapy: Preclinical data supports the use of genetically engineered iPSC-derived NK cells as promising clinical drug candidates to treat B-cell lymphomas

- To address the unmet need with autologous CAR-T related to safety or manufacturing issues, novel approaches are being investigated such as NK CARs. Key advantages include off-the-shelf availability, better safety, absence of GvHD, and without the need for full HLA matching.
- iPSCs are becoming an important starting cell source to derive NK cells based on the ease of genetic manipulation and indefinite expansion capacity.
- NK019 cells are engineered iPSC-derived NK cells therapy candidate differentiated from a modified human iPSC single-cell clone carrying three transgenes, including a CAR targeting CD19, a modified CD16, and an IL15 molecule that have showed promising in vivo activity.

FT516: Fate Therapeutics presented the positive interim data from Phase I study of universal FT516 NK cell therapy in combination with rituximab for B-cell lymphomas

- Derived from clonal master iPSC line that helps in mass production for faster availability.
- In heavily pretreated DLBCL, FT516 demonstrated an ORR of 73% and CR of 55%. Also showed a relatively favorable safety profile. No therapy-related ≥Gr3 AE, no CRS, neurotoxicity, or GvHD was observed with only rare febrile neutropenia.
- The study also permitted patients with prior CAR-T therapy.
- Interestingly, its administration did not require mandatory hospitalization during treatment, potentially due to improved safety. In future, these novel therapies may be given in outpatient settings.

Targets Beyond CD19 and Bispecific CAR-Ts

The tremendous success of CD19 monospecific CAR-Ts has a common limitation of acquired treatment resistance. The novel next generation of CAR-Ts moving towards dual targeting of two (or even more) tumor antigens simultaneously lending the bispecific CAR-T to be potentially more efficacious with the ability to overcome resistance due to antigen escape, the most common mechanisms of relapse after CAR-T therapy.

MB-106 (CD20 targeting CAR-T): Mustang Bio presented Phase I/II trial data in R/R NHL and CLL

- Shorter time of ~7 days from screening to treatment versus several weeks for auto-CAR-T.
- Promising clinical activity seen across NHL subtypes; overall high rates of ORR of 93% and CR of 67% at all dose levels. Favorable safety profile with no Gr3 CRS or neurotoxicity, only low-grade events seen. Gr3 febrile neutropenia was reported in 13.5% of patients.
- Prior treatment with CD19 CAR-T was permitted, suggesting a possible role in CD19 CAR-T progressors.

C-CAR066 (CD20 targeting CAR-T): Phase I first-in-human study targeting R/R NHL post CD19 CAR-T failure

- Shorter time of ~7 days from screening to treatment compared to autologous CAR-Ts.
- Demonstrated impressive clinical benefit; high ORR of 100% and CR of 70% and patients remain in CR for >10 months. Median DoR is not reached. Showed favorable safety profile with only low-grade CRS and no neurotoxicity was reported.
- Patients previously exposed to CAR-T were permitted, suggesting a possibility to provide an effective treatment option for CD19 CAR-T progressors.

C-CAR039 (CD20/CD19 dual targeting CAR-T): Phase I study evaluating 2nd generation CAR-T in R/R, B-cell NHL was presented.

- Promising outcomes include ORR of 92.6% and CR of 85.2% and 6-month PFS rate was 83.2% in 27 evaluable patients. Specifically, in DLBCL patients ORR was 91.7% and CR was 83.3%. Favorable safety profile was reported with only 1 Gr3 CRS, most CRS were low grade and reversible, no Gr3 neurotoxicity and rare cases of infections.
- Likely to provide an effective treatment option for CD20-refractory patients, which is a major unmet need in B-cell lymphomas.

Conclusion and Future Directions:

Cell therapies in hematologic malignancies are here to stay as an important treatment modality for treating B-cell lymphomas. The new wave of improved cell therapies will be a reality in the near term and can address the gaps and limitations of the current autologous CAR-Ts. The new data positions these therapies strongly vs. current SoCs though long-term durability of responses is yet to be seen. The relatively improved safety seen with these new generation of cell therapies may also help shift therapy to the outpatient setting.

Sources:

1. Locke FL, Malik S, Tees MT, et al. First-in-human data of ALLO-501A, an allogeneic chimeric antigen receptor (CAR) T-cell therapy and ALLO-647 in relapsed/refractory large B-cell lymphoma (R/R LBCL): ALPHA2 study [Abs# 2529]. In: ASCO 2021; June 4-8; Chicago. Available at: https://meetinglibrary.asco.org/record/196076/abstract.
2. Shah BD, Jacobson CA, Solomon S, et al. Preliminary safety and efficacy of PBCAR0191, an allogeneic, off-the-shelf CD19-targeting CAR-T product, in relapsed/refractory (R/R) CD19+ NHL [Abs# 7516]. In: ASCO 2021; June 4-8; Chicago. Available at: https://meetinglibrary.asco.org/record/197143/abstract.
3. Precision Biosciences Press Release. Precision biosciences reports progress on two strategies designed to optimize durability of allogeneic CAR T therapy in R/R non-Hodgkin lymphoma. Available at https://investor.precisionbiosciences.com/news-releases/news-release-details/precision-biosciences-reports-progress-two-strategies-designed. Published June 04, 2021.
4. McGuirk J, Bachier CR, Bishop MR, et al. A Phase I dose escalation and cohort expansion study of the safety and efficacy of allogeneic CRISPR-CAS9–engineered T cells (CTX110) in patients (PTS) with relapsed or refractory (R/R) B-cell malignancies (CARBON) [Abs# TPS7570]. In: ASCO 2021; June 4-8; Chicago. Available at: https://meetinglibrary.asco.org/record/201308/abstract.
5. NIH. A safety and efficacy study evaluating CTX110 in subjects with relapsed or refractory B-cell malignancies (CARBON). Available at: https://clinicaltrials.gov/ct2/show/NCT04035434.
6. Strati P, Bachanova V, Goodman A, et al. Preliminary results of a Phase I trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem cell (IPSC) line expressing high-affinity, non-cleavable CD16 (HNCD16), in patients (PTS) with relapsed/refractory (R/R) B-cell lymphoma (BCL) [Abs# 7541]. In: ASCO 2021; June 4-8; Chicago. Available at: https://meetinglibrary.asco.org/record/199035/abstract.
7. Yue Y, Song X, Zhou Y, et al. Genetically engineered IPSC-derived NK cells as a promising clinical drug candidate for the treatment of B cell malignant lymphoma [Abs#PB1542]. In: EHA 2021; June 9-17; Vienna. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324219.
8. Shadman M, Yeung C, Redman M, et al. Immunotherapy using a 3rd generation CD20 CAR-T-cell (MB-106) for B-NHL and CLL [Abs# EP731]. In: EHA 2021; June 9-17; Vienna. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/325491
9. Liang A, Ye S, Li P et al. Safety and efficacy of a novel ANTI-CD20 chimeric antogen receptor (CAR)-T cell therapy in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) patients after failing CD19 CAR-T therapy [Abs#2508]. In ASCO 2021; June 4-8; Chicago. Available at https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.2508
10. Liang A, Zhou L, Li P, et al. Safety and efficacy of a novel anti-CD20/CD19 bi-specific CAR T-cell therapy (C-CAR039) in relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) [Abs# 2507]. In: ASCO 2021; June 4-8; Chicago. Available at: https://meetinglibrary.asco.org/record/196090/abstract.

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