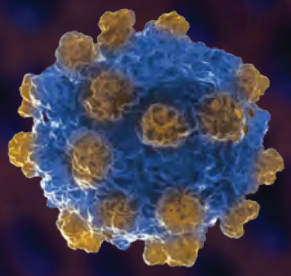

Rapid manufacturing: Speeding up access to effective CAR-T cell therapies

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment landscape for high-risk large B-cell lymphoma (LBCL) and relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) and large B-cell lymphoma (DLBCL), yet access to this treatment remains constrained by complex and lengthy manufacturing processes. The need for faster, more scalable production has led to new CAR-T platforms offering rapid and decentralized manufacturing to shorten "vein-to-vein" time while maintaining or even improving therapeutic efficacy. In this commentary, we look at the latest clinical advances of some of these platforms recently reported at ASH 2024 and EHA 2025.

Currently approved CAR-T cell therapies for R/R LBCL after at least two prior lines of therapy include axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel.

These therapies are produced using traditional manufacturing platforms that involve removal of the patient's own T cells (leukapheresis) and ex-vivo engineering of the cells in the laboratory to express a CAR. The cells are then reinfused into the patient, where they stimulate an immune response against the antigen-expressing cells causing the cells to die.

In clinical trials, the rates of objective response (OR) and complete response (CR) with these CAR-T cell therapies ranged from 52–83% and 40–65%, respectively[1-3].

Despite the overwhelming clinical benefit of these CAR-T cell therapies for patients who have aggressive disease and are often heavily pre-treated, their applicability is limited by:

1 The complex and long manufacturing process; which involves apheresis, T-cell isolation, activation using CD3 and/or CD28 antibodies, genetic engineering with virus vectors, expansion, and formulation. It often takes 2 weeks or more[4].

During this time a patient's condition could deteriorate necessitating bridging therapy and affect their eligibility for treatment[5].

2 Variable duration of response; relapse rates with traditional CAR-T cell therapies are around 30–60%[6]. CAR-T cell-related reasons for this include prolonged ex vivo T-cell expansion, which can lead to T-cell exhaustion and preferential proliferation of differentiated T-cells, or effector cells, at the expense of more desirable naïve, central memory, and T stem cell-like memory T cells, which are associated with a stronger and more persistent antitumor response[4].

3 Toxicities; namely cytokine-release syndrome (CRS), which can occur due to activated CAR-T cells releasing cytokines and causing a systemic inflammatory response, and neurological events, such as immune effector cell-associated neurotoxicity syndrome (ICANS), arising from immune activation. The rates of any grade and grade 3 or worse CRS with currently approved CAR-T therapies range from 42–93% and 2–20%, while the corresponding rates for ICANS are around 21–64% and 10–28%[1–3].

4 Accessibility and logistical issues; CAR-T manufacturing is primarily done in centralized specialist centers that may not be located where a patient is receiving treatment. While this offers standardization, quality control, and consistency, it also contributes to limited accessibility, long lead-in times, and the need for cryopreservation as potential drawbacks[4].

The need to overcome such barriers and accelerate the delivery of CAR-T cell therapy to make it more effective and widely available without increasing toxicity has prompted research into the current wave of new CAR-T cell therapy platforms. The latest findings for these have recently been reported at ASH 2024 in December and EHA 2025 in June.

Faster manufacturing and improved CAR-T cell quality

Phase 2 findings for rapcabtagene autoleucel (YTB323), a CD19-directed CAR-T cell therapy that uses the T-Charge™ (Novartis, Basel, Switzerland) next-generation platform have shown high response rates and a good safety profile in 63 patients with R/R DLBCL[7].

The T-Charge™ platform reduces the manufacturing time to less than 2 days, compared with the traditional 10 days. The CAR-T cell generation is largely done in vivo avoiding extended ex vivo cell culturing. This helps to preserve T-cell stemness, retaining naïve and T stem-like memory T cells for enhanced cell renewal, persistence, and antitumor activity. The aim being to achieve a vein-to-vein time of around 10 days rather than the standard 20 days[8].

According to the data, first presented at ASH 2024 in San Diego, California, USA, and shown as a poster at EHA 2025 in Milan, Italy, the OR and CR rates with a single infusion of 12.5 x 10^6 cells of rapcabtagene autoleucel over a median follow-up of 16.4 months were 88.3% and 65.0%, respectively, with around half of patients achieving a CR within 3 months. Progression-free survival rates at 12 months were 48% overall and 79% for patients who achieved CR within 3 months.

There were low rates of CRS (all grade, 43%; grade ≥3, 6%) and ICANS (all grade, 6%; grade ≥3, 3%).

And the shortened manufacturing time did not impede CAR-T cell expansion, which was robust with the in vivo method, giving a median maximum observed drug concentration of 41,800 copies/µg DNA.

Another previously reported rapid autologous manufacturing platform showing promise is FasTCAR-T. It has a manufacturing time of 1 day and has been tested in patients with R/R B-cell NHL using the CD19-BCMA dual targeting CAR-T product GC012F[9]. The first results were reported at ASH 2023 and showed 3-month OR rates of 100%, with CR rates of 77.8% at 3 months and 62.5% after 9 months with a single infusion of 3.7 x 10^4 to 3.0 x 10^5 cells.

Grade 1 CRS occurred in five patients and there was one case of grade 3. There were no incidences of ICANS.

The median maximum number of CAR-T cells in the peripheral blood was 71,000 copies/µg DNA.

Comparison of response rates across the CAR-T products

CAR-T Product	Pivotal Trial	ORR (%)	CRR (%)
Axicabtagene ciloleucel	ZUMA-7	83	65
Tisagenlecleucel	JULIET	52	40
Lisocabtagene maraleucel	TRANSCEND NHL 001	73	53
Rapcabtagene autoleucel/T-charge™	NCT03960840	88	65
GC012F/FasTCAR-T	ChiCTR2100047061	100	79
GLPF5101/ Cocoon®	ATALANTA-1	88	83
CliniMACS Prodigy®	ACIT001/EXC002	79	68

OR: objective response rate; CR: complete response rate

Allogeneic strategies to avoid leukapheresis

Allogeneic techniques that use T cells from healthy donor peripheral blood rather than the patient's own and thereby avoid the need for leukapheresis and ex vivo expansion are also being explored as a means of rapid manufacturing. Two such platforms – UF-Kure19 and MARS Atlas – were also presented at ASH 2024. Although at early stages of development, they boast a CAR-T product that is available within 24 hours[10,11].

UF-Kure19, a second-generation 4-1BB CAR, at a dose of 17.5 x 10^6 cells was tested in a phase 1 study of 10 patients with R/R NHL, including mantle cell lymphoma (MCL; n=2), follicular lymphoma (FL; n=4), DLBCL (n=3), and plasmablastic lymphoma (n=1).

Even with the fast turnaround and no ex vivo expansion, the naïve, central memory, effector memory, and late effector cell percentages in the infused product were consistent with pre-apheresis levels.

The CR rate at 6 months was 80%. CRS, of grade 1–2, occurred in only three (30%) patients and grade 3 ICANS, which resolved within a day, occurred in just one (10%) patient. These low rates may be related to the fact that in vivo CAR-T cell expansion took a little longer to peak compared with standard CAR-T products, the researchers suggest, being first detected after 2 days and reaching 7.07% at 21 days.

Proliferation of CAR-T cells above measurable levels occurred only in patients who achieved remission. B cell aplasia was noted in all patients after 30 days, and circulating CAR-T cells persisted at more than 1% of T cells in all responders, including for up to 12 months post-infusion in one patient.

The MARS Atlas platform integrates T cell isolation, viral transduction, and cell washing/formulation processes using donor peripheral blood to produce CAR-T cells within 24 hours. It was tested against a standard 7-day process involving ex vivo expansion of transduced T cells in culture.

After 24 hours, the researchers were able to harvest 20 x 10^6 T cells per 30 mL of blood using the platform with a purity of more than 94%. The T cells produced had twice as many naïve T cells as those harvested after the 7-day process and the percentage of cells successfully expressing CAR was high at 60–70%.

The ability of the CAR-T cells manufactured using the rapid process to kill target cancer cells was confirmed by in vitro assays at day 7.

Decentralized manufacturing for wider applicability

The aim of decentralized manufacturing is to bring the production of CAR-T therapies closer to the point of care by simplifying the process, minimizing or eliminating the need for cryopreservation, and reducing the vein-to-vein time – from leukapheresis to infusion of the CAR-T cells. This is achieved by combining automation, digital technologies, and a modular approach that can be used in healthcare facilities[5].

One such technique being tested in patients with R/R NHL is GLPF5101, which is a fresh, stem-like, early memory phenotype anti-CD19 CAR-T cell therapy manufactured using Cocoon®, (Lonza, Basel, Switzerland). This is a decentralized, functionally closed, automated manufacturing platform.

Findings from the ongoing phase 1/2 trial of GLPF5101 – ATALANTA-1 – were first presented at ASH 2024, with further updates reported at EHA 2025[12,13].

The manufacturing process involves leukapheresis on day 7, standard conditioning chemotherapy on days 6 to 4 and then a 3-day washout period before a single infusion of GLPG5101. A 7-day vein-to-vein time and infusion of fresh product was achieved in the majority of the 64 R/R patients, comprising 17 with DLBCL, 12 with MCL, 27 with FL, and five with marginal zone lymphoma (MZL). This was associated with a low attrition rate after leukapheresis of 4.7%, compared with previously reported clinical trial rates of up to 30%[14].

Among 42 evaluable patients available at data cut-off (median 13 months), the OR rates were high, at 69% in DLBCL patients, 95% in FL and MZL patients, and 100% in MCL patients, with corresponding CR rates of 54%, 95%, and 100%.

There was only one case each of grade 3 or worse CRS and ICANS, occurring at a median of 7.0 and 11.5 days, respectively, which lasted for just 2–3 days.

Evidence supporting a decentralized manufacturing approach was also reported at ASH 2024 from the phase 1b/2 ACIT001/EXC002 trial testing anti-CD19 CAR-T therapy using the CliniMACS Prodigy® (Miltenyi Biotec, Surrey, UK) automated platform[15].

Among the 30 participants in the ACIT001/EXC002 trial who had received a minimum of two prior lines of therapy – 23 with NHL (five transformed; five with central nervous involvement) and seven with acute lymphoblastic leukemia (ALL) – the vein-to-vein time was a median of 14 days (range 14–28 days). Ninety-three percent of patients received fresh product.

The overall OR was 79%, with CR achieved by all the ALL patients and 58% of the NHL patients. Over a median 16 months of follow-up, 18 patients were still in remission. Fifty-five percent of patients had grade 1 or 2 CRS, with no cases of grade 3 or higher, while grade 1 or 2 ICANS occurred in 14% of patients.

By streamlining cell processing and reducing vein-to-vein time, rapid manufacturing CAR-T platforms have the potential to improve treatment access and convenience and reduce lead-in times for more enduring treatment. As research continues and evolves, it will be important to balance this faster, decentralized manufacturing with consistent quality control, maintained CAR-T functionality and persistence, and low toxicity.

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