Cellular Therapy and Transplantation (CTT). Vol. 13, No. 1, 2024
doi: 10.18620/ctt-1866-8836-2024-13-1-6-15
Submitted: 10 January 2024, accepted: 01 March 2024

Towards personal gene and cell therapy: accelerating factors and roadblocks on point-of-care production approach

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Citation: Samsonov MY, Lomonosov AM. Towards personal gene and cell therapy: accelerating factors and roadblocks on point-of-care production approach. Cell Ther Transplant 2024; 13(1): 6-15.

Summary

Recent advances in gene and cell therapy showed impressive results over last decade that culminated into approval of CAR-T therapies, i.e., long-term remissions in hopeless cancer patients that may be considered curative in the number of cases. These developments brought us to the recent gene therapies for such inherited disorders as beta-thalassemia and Duchenne myodystrophy. However, access of the patient to such life-saving therapies is still very limited, due to extremely high pricing and some bottlenecks specific for the personalized production approach. Efficacy of personalized therapies presents a challenge to the centralized manufacturing model which is commonly accepted by pharma and regulators and may self-limit its development. We discuss current evidence in favor of novel promising ways for cell and gene therapy (CGT), i.e., point-of-care (POC) manufacturing as a developing trend in its clinical applications. It is demonstrated that POC production by academic facilities may be approved for clinical use, being even more effective than commercial products, due to higher production speed, percent of successful manufacturing and lower total production costs, if the new regulations are applied. Examples of successful POC CAR-T therapies are even more important in view of new data on the highly efficient implementation of single-shot CAR-T therapies in autoimmune diseases, including systemic lupus erythematosus (SLE) and severe myasthenia, followed by long-term remissions which do not require any additional treatment.

Keywords

Cellular therapy, CAR-T cells, pricing, access, regulations, point-of-care production.

Introduction

Advances of gene and cell therapy of last two decades have resulted into FDA approval of tisagenlecleucel (Kymria) in 2017 as the first product for CAR-T therapy in pediatric B-cell acute lymphoblastic leukemia, finally showing impressive clinical results. In particular, the CGT approach has produced long-time cancer remissions in cases refractory to any available treatments, becoming curative for some patients [1, 2]. This single-injection treatment for previously incurable patients has been marketed by Novartis, the leading pharma company, thus finally opening the road to therapies, based on gene or cell engineering approaches, which were "on hold" by regulators and industry for a long time. Since then we have 6 approved items for CAR-T therapies [2], with CD-19 and BCMA as molecular targets for chimeric antigen receptors, thus allowing treatment in patients with refractory B-cell acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma (LBCL), relapsed and/or refractory (R/R) follicular lymphoma (FL), mantle cell lymphoma (MCL) with CD-19 expression, and in multiple myeloma (MM) for BCMA-targeted cells.

The regulatory improvements in the gene and cell therapy and industry guidance by leading regulators have catalyzed other key approvals in the field: we have seen first accepted gene

therapies of rare genetic diseases, including Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), Hereditary Transthyretin-related Amyloidosis, Hereditary homozygote blindness, beta-thalassemia, as well as recently approved therapies against sickle cell disease, including the CRISPR/Cas9-based Casgevy product [4]. These approvals are quite important, covering almost all modalities of gene and cell therapies for distinct life-threatening and rare disorders. However, there were two drug approvals in the field of RNA therapeutic products for treatment of common human diseases (except of multiple RNA-based COVID vaccines) thus suggesting that we are approaching a tipping point in wide range of common disorders. E.g., a possible shift from daily drug administration to once-a-6 month injection was shown by Leqvio (inclisiran), an RNA antisense therapeutic used in hyperlipidemia, that demonstrating feasibility and cost-effectiveness of such drugs at the larger scale [5].

This is an opportunity, or emerging trend that may dramatically change general healthcare and, in particular, pharma business models. The future looks bright according to the Q3 2023 ASGCT report [3] reviewing present state of gene and cell therapies. Currently, there are 3,866 therapies under development. Of them, 53% concern gene therapies (share of CAR-T cell products); 25% are RNA-based preparations, and 22% represent therapies with non-gene-modified cells.

Current challenges

Hence, the trend for a personalized, highly effective, single-injection CGT is very attractive. This treatment mode is available for as long as 5 years. Do we still have revolutionary changes with respect to the numbers of patients treated, and, especially, acceptance of high price for such therapies by the payers?

The more therapies are coming to market, the higher they are priced, as shown by simple linear analysis (Fig. 1). The 2023 data on drug approvals again hit the roof with 3.2 mln USD per injection of Elevidys (delandistrogene moxeparvovec) for DMD therapy thus continuing the price of 3,5 mln USD (2022) *per* a single injection achieved by Hemgenix (etranacogene dezaparvovec) for Hemophilia B treatment. Even despite administration of these drugs in orphan diseases, the overall pricing trend raises the issue of treatment accessibility. Indeed, CAR-T therapy, with longest track record on the market and three Big Pharma players (Gilead, Novartis and BMS) could reach therapy for only about 33,000 patients globally from 2017 [6]. Moreover, when looking on sales growth for CAR-T cell products (Table 1), one may see that Kymria sales declined in 2022, indicating that overall CAR-T market possibly is close to reaching its limit. The emerging competition may sufficiently affect sales, even though a small proportion of eligible patients will receive this therapy.

It should be noted that the annual sales for CD19 targeted CAR-T Kymriah declined in 2022, sales of most commercially successful CD19-targeted CAR-T cells (Yescarta) are lower than those for Zolgensma, the first tool for therapy of SMA, a rare genetic disease: it also seems to reach its sales limit in 2022 (Table 1).

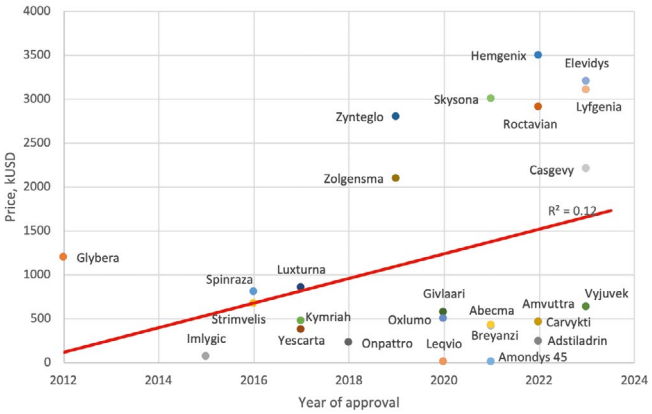

Figure 1. Drug pricing in New Gene and Cell therapy (2012-2023). Abscissa, years of approval. Ordinate, prices for newly approved gene and cell therapy brands (thousands of US dollars).

Every point refers to price of a single GCT injection/infusion for single-shot agents. In case of several injections/infusions *per* treatment course (i.e., in some chronic conditions), the one-year price estimates are shown. This graph is based on the price data analysis from open sources [7, 8]. The trend line for prices of CGT therapies is based on a standard linear approximation model.

Table 1. Annual sales of selected gene and cell therapies (GCTs) over 2019 to 2022

GCTs sales, mln USD	2019	2020	2021	2022
Kymriah (CAR-T)	287	474	587	536
Yescarta (CAR-T)	456	563	695	1160
Zolgensma (Gene therapy)	361	920	1351	1370

*Data of annual sales volumes were prepared by authors based on public financial reports of Novartis and Gilead companies.

Another problem that affects accessibility for GCT treatments is clearly seen by examples of approved CAR-T cell treatments: the general production strategy which employs big production sites is very expensive to build, thus intending to meet the demands from several countries [9].

The manufacturing of CAR-T cells starts with leukapheresis in a certified medical center followed by delivery of frozen patient's cells to the production site, where an appropriate time slot for the production should be allocated first. Thereafter, the cells are quality-checked, isolated, activated, transfected with CAR vector, expanded, assigned to particular cell number, quality-controlled (QC) in order to ensure efficacy, potency and safety of the cell product. The cell preparations are cryoconserved and delivered back to the medical center where CAR-T cells are finally infused to patient. This process, as assigned for the two leading market products, Axicabtagene ciloleucel and Tisagenlecleucel is reported to have target median turnaround times of 17 and 22 days respectively [10, 11]. However, this timing may be increased up to 2 months [11]. Approval of medical center prior to start providing a CAR-T cell therapy is critical, since the cytokine release syndrome is the most common adverse effect which is a well manageable but life-threatening event. Leading regulators (FDA and EMA) require Risk Evaluation Mitigation

Strategy (REMS) or similar procedures to be implemented in medical centers providing CAR-T therapy, being a substantial obligation from medical center [11] thus limiting the number of centers authorized for CAR-T (or other advanced CGT) therapies. However, the overall production process starting with slot allocation may be much longer.

All these factors form a set of barriers on patient journey to receive CAR-T cell (or, in general, any expensive CGT) therapy. Analysis of CAR-T therapy for diffuse large B-cell lymphoma (DLBCL) was performed in Italy where it is covered by state insurance program [12]. The authors revealed that only 17% of patients received this treatment in 2020 among ca. 600 patients eligible for CAR-T cell therapy by EMA label indication. 83% of the patients were lost in this funnel, due to multi-level medical, financial, logistic obstacles, and other steps that is required by CAR-T therapy [10, 11].

Otherwise, we must accept usage of personalized CGT therapy according to the "one-fits-all" paradigm. Research on real-life clinical outcomes of commercial CAR-T therapies Axi-cel or Tisa-cel [26] showed that 7% of patients after apheresis did not receive this treatment due to different factors, like as in other clinical trials in the field [12]. This pharma production paradigm remains quite effective to provide non-personalized drugs. However, direct application of this paradigm seems to be not ideal and self-limiting for GCT therapy which presumes a personalized treatment in most cases. Main reason is expenses. If we look at expenses that are associated with bringing new CGT therapy to market, even taking into account all the supportive measures from leading regulators, for example, FDA-hosted programs as *"Accelerated approval", "Breakthrough therapy" and "Orphan" designations*, it doesn't dramatically affect the development costs [13, 14]. Appropriate expenses to bring new CGT therapy into the market are about 1,5-2 bln. USD *per* a single approved drug therapy, and the overall trend is still rising despite >50% of newly approved drugs are covered by such support measures [15].

This leads to vicious circle of personalization, which is briefly depicted in Fig. 2. It reflects the current approaches to CGT. A conventional strategy of drug development and usage by pharma companies, if applied to personalized drug therapies, will automatically lead to be extremely high expenditures and very limited patient access. Indeed, drug personalization leads to decrease of patient population that can be treated by particular drug, and distinct batch of produced drug in case of personal medication. This trend, due to unchanged or even growing expenses, when trying to reach the market for a single drug, with high expenses of personalized production by a pharma company, leads to increase of calculated price *per* patient. Such situation becomes more obvious in case of one-shot curable treatments like some CAR-T therapies. As a result, the expense-driven setting of too high prices for treatment may be justified only for very limited number of clinical cases, which again leading to decrease in potential number of patients to be cured, thus closing this vicious circle.

Currently, there are three ways to resolve this self-limiting circle: (1) development of non- or less personalized CGT, e.g., Leqvio (inclusiran), an RNA-based drug; (2) justify high price using pharmacoeconomic approaches, as it is done by all marketed drugs (with few exceptions, i.e., of Glybera, Zynteglo and Skysona, that was withdrawn in EU by commercial reasons [16]); (3) usage of special regulatory pathways like "hospital exemption", "compassionate use" etc, thus allowing development of drugs by academic labs, in order to produce the medication and provide its clinical approval at dramatically reduced costs.

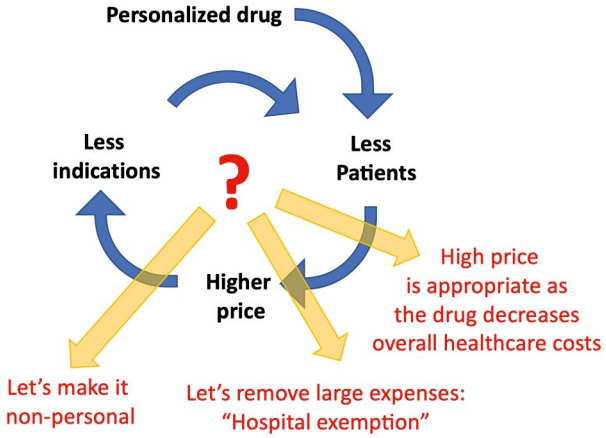

Figure 2. Vicious circle of personalization in drugs development and production within current centralized production paradigm. The picture shows some interdependencies in development of new drug by pharma companies, and reflects an approach to avoid both patient-based and commercial limitations.

On the contrary, we may refer to interesting results of modeling analysis being most impactful for both society health benefit and pharma companies. I.e., only 10% increase in patient eligibility and access to CGT therapies in rare blood diseases may lead to an estimated increase of savings for payers over $3 billion by 2029 [17]. For the pharma companies, potential patient number and time to market are crucial for commercial success, aiming for successful delivery of novel CGT therapies to the market and return of investments [18].

Point-of-care options

Point-of-care CGT production seems to be a powerful way to expand the eligible patient cohort, to decrease price of treatment and improve patient access, and to speed up development of the product [19]. Indeed, small-scale GCT production, e.g., CAR-T cells for the personalized cell-based therapy at a single academia center might be adequate for needs of its patients. Due to origin of such product, it is manufactured personally for each patient, either being produced at a big factory or at a small cell lab at a clinical facility, when keeping proper quality control measures. Moreover, in case of such point-of-care (POC) manufacturing, there are no issues with logistics, any delays and treatment failures due to changes in clinical condition of the patients. Hence, it may dramatically reduce the vein-to-vein time down to 8 days [19], and the cell product would act more effectively since its viability is better preserved. However, quality of cell products and regulatory approvals cause biggest concerns with POC manufacturing of CGT preparations.

Quality assurance is required to provide a clinical grade product, including good manufacturing practices (GMP-grade processes) with validated raw materials (i.e., cell culture media, cytokines and other reagents, as well as leukapheresis products), and certified clean rooms. These requirements can be met at a large number of academia centers due to several factors: 1. Research spillover due to infrastructure, skilled personnel and knowledge acquired during previous grant-funded studies in CGT which be used in further production at GMP-grade clean rooms and equipment assigned for preclinical and early clinical trials [20, 21]; 2. Wider approval and utilization of closed automated cell-production systems like Miltenyi Biotec CliniMACS Prodigy® and Lonza Cocoon® [17, 19], as well as new products from China, like Sino-Biocan Wukong [22], that provides modular automated cell production, that are much less sensitive to clean room conditions and operator experience, being already supplied with GMP-grade consumables, thus providing high-success rates of CAR-T cells production. In Russia, there are also promising developments in this filed [23].

Ability for many academia centers to provide high-quality POC production is successfully used to prepare efficient cell products for clinical trials. A number of such academia CGT production centers, at least in Europe, were used to get clinical evidence for adoption of currently marketed CAR-T therapies [9]. A number of clinical trials demonstrate comparable or even better clinical results compared to previously approved CAR-T cell therapies (Table 2).

Clinical experience

Significant amount of real-world evidence (RWE) with commercial CAR-T products (see Table 2) demonstrates a very similar performance of such products in real-live setting and 2nd phase clinical trials. These data were mostly used as the basis for clinical approval. We can see it for tisagenlecleucel (tisa-cel, Kymriah, Novartis) and axicabtagene ciloleucel (axi-cel, Yescarta, Gilead). Comparison of these products, despite significant superiority over conventional therapy, shows some differences in response rates, overall survival, and intensity of typical CAR-T adverse events (e.g., CRS and ICANS). This body of evidence was also supported by direct RWE comparisons in DLBCL patients: ORR of axi-cel of 80% *vs* 66% with tisa-cel, and CRR of 60% *vs* 42% for patients treated with axi-cel *vs* tisa-cel. One-year PFS was 46.6% and 33.2% for axi-cel and for tisa-cel, respectively. One-year OS was also improved after axi-cel infusion compared to tisa-cel. Interestingly, the real-world evidence studies for tisa-cel [25, 26] demonstrate that about 10 to 30% of patients received an out-of-specification product, with reduced cell viability (>20% loss), still showing a comparable clinical benefit.

The results shown in Table 2, demonstrate some differences between the two most mature commercial CAR-T products. Moreover, this evidence promotes current advances in methodology of CAR-T clinical trials or, more generally, CGT trials, by enabling high predictability on safety and efficacy at rather small sizes of patients' groups. Of note, the data from clinical trials were rather limited but they permitted approval for the both therapies, i.e., Kymriah was approved on the basis of ELIANA clinical trial with 75 patients, and Yescarta has been proven with 108 patients from ZUMA-1 trial and 68 patients of ZUMA-2 trail only [2, 27, 28]. These group sizes would be sufficient to obtain approvals of the POC therapy for academia clinical centers, if such mode of action is acceptable to the regulator.

This is important due to growing number of successful POC clinical trials, which seem to show comparable results and may declare even better results than those observed with commercial products. These results may be promising with superior clinical outcomes over centralized commercial CAR-T production model.

Some examples of POC CAR-T cell therapy are worthy of mention. A work by Maschan et al. [29] has demonstrated an opportunity of decentralized POC CAR-T production with single protocol at two academia clinical sites, i.e., in Moscow (Russia) and Cleveland (USA), based on automated closed-cycle production using CliniMACS Prodigy®) systems with CAR19-T cells manufactured at stable quality under current good manufacturing practices (cGMP). The results of two independent Phase 1 clinical trials in relapsed/refractory pediatric B-cell acute lymphocytic leukemia (ALL; $n = 31$), or adult B-cell lymphoma (NHL; $n = 23$) were as follows: complete remission (CR) rates were 89% (ALL), and 73% (NHL). After a median follow-up of 17 months, one-year survival for ALL complete responders was 79.2% (95%CI 64.5-97.2%). For NHL complete responders, one-year survival was 92.9%. Importantly, the manufacturing success rate exceeded 96% with automated closed-cycle production system used at two different sites in distant countries, at the median apheresis-to-infusion time of 13 days, thus sufficiently outperforming commercial CAR-T cell products.

Sheba Medical Center developed POC CAR-T product to treat aggressive B cell lymphoma (ABCL), with CAR construct designed to lower toxicity [30]. Clinical trial with 73 patients has shown a shortened CAR-T cell production time from apheresis product (a mean of 10 days only), that allowing to avoid bridging chemotherapy. Overall survival rate was 62.5%, with complete response rate (CRR) of 37.5%, median progression-free survival (PFS) of 3.7 months, and median OS of 12.1 months. OS rate at 12 months was 52.1% (CI: 40.8%-66.5%) and PFS, 40% (CI: 30%-53.7%). Grade 3-4 cytokine release syndrome (CRS) was observed in 9.5% of the patients, and ICANS grade 3-4 was documented in 21.9%. In general, these data demonstrate similar efficacy and safety to commercial products. Along with rather short vein-to-vein time, production efficiency was 98.6 %, and all the screened patients were eventually treated with CAR-T cells, that suggesting its superiority over commercial model with around 10% cell losses after apheresis. Based on results of clinical trials, POC CAR-T therapy in this center was approved by Israeli Ministry of Health, and currently priced 30-80% less than commercial CAR-Ts with >200 patients infused [31, 32]. Interesting application for in-house made POC CAR-T cells has been suggested at Sheba Center. The patients underwent salvage therapy and were scheduled for tisa-cel-treatment, being, however, supplied with out-of-specs (OOS) cell products [33]. This study showed that 24% of OOS are observed in real-life setting, and POC products

Table 2. Clinical performance of commercial and academia-developed CAR-T products

Treatment	Patients number in clinical trial/clinical data	Outcomes	Safety	Reference No.
Commercial CAR-T products real-life performance (based on RWE studies)				
axicabtagene ciloleucel (Yescarta, Gilead)	r/r LBCL – 1297 pts (RWE)	ORR – 73% CRR – 56% 1 year OS – 62% 1 year PFS – 47%	CRS 83%, Grade 3,4 – 8% ICAN – 55%, Grade 3,4 – 24%	24
tisagenlecleucel (Kymriah, Novartis)	pediatric/young adult ALL – 255 pts (RWE);	ORR – 85% CRR – 85% 1 year OS* – 77.2% 1 year PFS* – 52%	CRS 55%, Grade 3,4 – 16% ICAN – 27%, Grade 3,4 – 9% 10-30% received out-of-specification product	25
axicabtagene ciloleucel (Yescarta, Gilead)	RWE Comparative study with 809 DBLCL pts	ORR – 80% CRR – 60% 1 year OS – 63.5% 1 year PFS – 46.6%	CRS 86%, Grade 3,4 -5% ICAN -49%, Grade 3,4 – 13%	26
tisagenlecleucel (Kymriah, Novartis)		ORR – 66% CRR – 42% 1 year OS* – 48.8% 1 year PFS* – 33.2%	CRS 75%, Grade 3,4 – 9% ICAN – 22%, Grade 3,4 – 3%	
Commercial CAR-T registrational trials				
axicabtagene ciloleucel (Yescarta, Gilead), ZUMA-1 Trail	r/r LBCL – 101 pts	ORR – 83% CRR – 58% 1 year OS – 60,4% 1 year PFS – 44.6%	CRS 93%, Grade 3,4 – 11% ICAN – 64%, Grade 3,4 – 30%	27
tisagenlecleucel (Kymriah, Novartis), ELIANA Trail	pediatric/young adult ALL – 79 pts	ORR – 82% CRR – 62% 1-year OS* – 77.1% 1 year PFS* – 38%	CRS 77%, Grade 3,4 – 49% ICAN – 39%, Grade 3,4 – 13%	28
Academia CAR-T performance				
CAR19-T cells, Maschan et al.	r/r B-cell ALL, 31 pts	CRR – 77% 1-year OS – 67% 1-year PFS* – 29%	CRS 57%, Grade 3,4 – 7% ICANs – 43%, Grade 3,4 – 13% Manufacturing success 96%	29
	NHL, 23 pts	ORR – 83% CRR – 70% 1-year OS – 77% 1-year PFS* – 56%	CRS 52%, Grade 3,4 – 4% ICANs – 22%, Grade 3,4 – 9% Manufacturing success 96%	
Sheba medical center developed point-of-care (POC) CAR T-cell product	ABCL – 73 pts	ORR – 62,5% CRR – 37.5% 1-year OS – 52.1% 1-year PFS*- 40%	CRS 85%, Grade 3,4 – 9% ICANs – 39%, Grade 3,4 – 22%	30
ARI-0001 Hospital Clinic de Barcelona	>25 years old r/r ALL – 38 pts	CRR – 84% 1-year OS – 69% 1-year PFS- 47%	CRS 55%, Grade 3,4 – 13% ICANs Grade 3,4 – 2,6%	36

Abbreviations: ORR, overall response rate; CRR, complete response/remission rate; OS, overall survival; PFS, progression-free survival; AE, adverse events; CRS, cytokine release syndrome; ICAN, immune effector cell-associated neurotoxicity syndrome; LBCL, relapsed or refractory (r/r) large B cell lymphoma; r/r ALL, relapsed/refractory acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; ABCL, Relapse of aggressive B cell lymphoma; NHL, B cell non-Hodgkin lymphoma; RWE, Real world evidence.

may benefit in the patients who cannot wait for another lot of CAR-T cells. POC approach also allows fast clinical development for other indications, i.e., new molecular targets. This opportunity is supported by promising results on the CAR-T cells targeted against BMCA in relapsed/refractory multiple myeloma [34], developed in Sheba Center, using similar genetic CAR construct backbone and the same production facilities. The pilot study showed an estimated 6-mo OS of 89% (95% CI: 75-100), PFS of 48% (95% CI: 33-72), with no bridging therapy required in most cases. Additional advantage of POC production is ability to fast extension of clinical indications for therapy, as proven by the same clinical team who demonstrated good results of anti-CD19 CAR-T therapy to treat relapsed/refractory follicular lymphoma [35]. At enrollment, the disease stage was III-IV in 85% of the patients (n=26), with 77% having high-risk FLIPI score, and 77% were in progressive disease. ORR at 1 mo was 88%, with one-year OS of 100%, and PFS rate of 63%.

Another important success story of POC CAR-T therapy is ARI-0001, launched at the Hospital Clinic de Barcelona, employing an automated closed CliniMACS Prodigy cell processing system (Miltenyi Biotec). In February 2021, this product received authorization by European regulations as

an ATMP (advanced therapy medicinal product) from the Spanish Agency of Medicines and Medical Devices under the 'hospital exemption' (HE), according to EC Regulation No 1394/2007 (article 28.7), for the treatment of patients >25 years old with relapsed/refractory acute lymphoblastic leukemia (ALL) [2]. Interestingly, this is the first approved CAR-T product, developed in EU. The following results were obtained at Phase 1 clinical trial of ARI-0001 [36], on which the HE approval was based: of 58 patients included, 47 received the therapy, which resulted in 1-year PFS of 47% (95% IC 27%-67%), and OS of 68.6% (95% IC 49.2%-88%). In ALL patients, the grade ≥3 cytokine release syndrome (CRS) was observed in 13.2%; grade ≥3 neurotoxicity was registered in 2.6% of the cases. The last proportion is significantly lower *versus* commercial products. Cell production time varied between 7 to 10 days. However, the average vein-to-vein time was 42 days, due to complications and requirements of 2nd apheresis procedure in 14% of patients. Of note, this shows flexibility of POC approach, that allows to adapt for lower number of produced CAR-T cells by adding 2nd production cycle for the same patient, which is difficult or not feasible in the centralized production paradigm.

Similar to the mentioned approach used in Sheba clinic, POC production of CAR-T cells allowed fast launch of BMCA-targeted CAR-T therapy of multiple myeloma using the same backbone CAR construct and ARI0002h, a humanized BMCA antibody [37] for phase 1 clinical trial. 35 patients from 5 centers were enrolled in this trial, of which 86% received ARI0002h. With median follow-up of 12.1 months (IQR 9,1-13,5), OR was 100% during the first 100 days from infusion; CR rate of 50%, and partial remission (PR), in 50% of cases. Grade 1-2 CRS was registered in 80% of patients, and, notably, no neurotoxic events were observed. Of note, price for ARI-0001 was around 30% of commercial CAR-T products available in Spain [38].

An interesting collaboration experience extended into volunteering organizations has been reported by Canadian consortia [39], consolidating several clinical and research centers (Vancouver, Victoria and Ottawa) that were able to manufacture CD-19 CAR-T cells by CliniMACS Prodigy system (Miltenyi Biotec). The challenge was successfully resolved by manufacturing CAR-T product without cryopreservation, with 15 days vein-to-vein time and at the distances of up to 4300 km between the production site and clinical centers, by non-commercial academic sites and volunteer couriers. Thirty-five patients with CD19-positive hematologic malignancies were enrolled in CLIC-01 clinical study of non-cryopreserved CLIC-1901 CAR-T cell product, and 30 patients received the cell product infusion. Even despite some limitations in clinical interim results, one should note ORR of 77% at day 28, with median OS of 11 months, median PFS of 6 months. The manufacturing failure rate was only 6% (2 of 35). Grade >3 adverse events, mainly CRS, were registered in 7% (2 pts), and ICANS was observed in 3% of cases (1 pts). This result demonstrate that CAR-T technology in automated closed-cycle systems may provide robust results and fast vein-to-vein time even at long transportation routes. Hence the consortia of academia institutions can also resolve the issues related to CAR-T cell production, even upon delivery of fresh cells without cryopreservation.

These examples demonstrate both the ability for academia-based POC CAR-T cells to produce clinically beneficial results being comparable with commercial products, however, at significantly lower price and increased operational flexibility.

The mentioned factors are increasingly important, since new applications for CAR-T therapy in autoimmune diseases showed very promising results, mostly in academia setting using POC CAR-T cell production. Specific feature of systemic autoimmune diseases is production of autoantibodies and autoreactive T lymphocytes, which damage organs and tissues and cause various symptoms which may limit everyday normal life, and are able to cause life-threatening conditions. These disorders are caused by cytotoxic autoantibodies, and autoreactive cytotoxic T lymphocytes (CTLs) that recognize target cells and damage it. In this respect, very promising results were shown in limited clinical trials on systemic lupus erythematosus (SLE), idiopathic inflammatory myositis (IIM), systemic sclerosis (SSc) rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis (MG) and other autoimmune disorders [40]. One should note that such diseases affect millions people worldwide, and effective therapeutic options are limited by their choice and efficacy. E.g., systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by adaptive immune system activation, formation of double-stranded DNA (dsDNA) autoantibodies and organ inflammation, which affects more than 3.4 million people worldwide. Quite promising results were obtained by European research team, when treating SLE patients with CD-19 targeted CAR-T cells [41, 42]. Five patients with SLE, refractory to several immunosuppressive treatments enrolled in a compassionate-use CAR-T program, have shown a deep depletion of B cells, improvement of clinical symptoms, including decrease in anti-dsDNA antibodies. Remission developed within 3 month, and drug-free remission was maintained >8 months after CAR T cell treatment, being not affected by reappearance of B cells. The treatment was accompanied by low-grade CRS.

Another CAR-T cell-based treatment in SLE was successfully applied in Phase 1 clinical trial in China [43], where the researchers aimed to overcome possible drawbacks of single CD19-directed CAR-T cells, e.g., inability to clear CD19-negative, long-lived plasma cells, which also produce numerous antibodies. According to published results of clinical trial, twelve refractory SLE patients were treated with autologous anti-CD19 and anti-BCMA CAR-T cells. After lymphodepleting chemotherapy, the patients received a single infusion of CD19 CAR-T cells and BCMA CAR-T cells. Median follow-up time was 118.5 (45-524) days. All patients developed grade 1 CRS, and no ICANS. The SLEDAI-2K score decreased in all patients, from a mean of 18.3 to 1.5 points. All patients could successfully discontinue all SLE-related medications, and remained in drug-free remission by the date of report. Now there are >14 clinical trials of CAR-T therapies only in SLE patients [44]. However, there are more examples of different autoimmune diseases, that may be brought into remission by POC CD-19 CAR-T treatment.

MB-CART19.1, a product developed by Miltenyi Biotec, being not yet approved, apart from being used in numerous

oncology-related clinical trials, was also successfully used in 15 patients with severe autoimmune diseases (8, SLE; 3, IIM, and 4 with SSc), with a single infusion of anti-CD19 CAR-T cells based on compassionate use approach [45]. Median disease duration before CAR-T therapy was 3 years, and all patients failed to respond at previous treatments. As a result of CAR-T therapy, CD19+ cells were eliminated in all patients, however, re-occurred later. Nonetheless, all SLE patients reached complete remission, all IIM patients showed normalization of CK levels; SSC patients demonstrated significant disease improvement, and importantly, all patients stopped immunosuppressive drugs. Safety of CAR-T cell therapy was very good, CRS of Grade 0-2 was observed in all patients, one patient experienced grade 1 ICANS.

The same approach was used, again as a POC protocol with CD19 CAR-T cells, with ClinMaxProdigy automated system from Miltenyi Biotec, in order to successfully treat patient with refractory antisynthetase syndrome, a rare immune disease from group of Idiopathic inflammatory myopathies [46]. In this single patient, a complete and long-lasting resolution of symptoms was observed, i.e., improvements in sit-to-stand test (from 0 to 7 after 6 months) and in maximal walking distance (10 m before therapy to >5km after 6 month).

A recent comprehensive review in *Nature* has summarized fast development of CAR-T therapies in autoimmune disease, showing very a promising approach, specifically feasible in academia setting. When immunologists meet the needs of oncologists and prepare CAR-T treatment for their patients with common cellular target (B-cells), this collaboration leads to very fast and "mind-blowing" clinical results with already proven safety and potential clinical efficiency [47].

Regulatory agencies and POC manufacturing

Recently, FDA had issued recommendations for distributed manufacturing and Point-Of-Care Manufacturing [48], describing approaches to regulatory approval of such approaches, however not yet being a guidance for industry. Hospital exemption rules are working in EU, with several products approved under it, including CAR-T cells. In Russia, new amendment to regulation on biomedical cell products had been enacted recently, and a complete set of regulations for POC should appear in 2024 [49]. Similarly, Switzerland has created a distributed framework for CAR-T cell production. UK is in the process of establishing legislation for localized cell manufacturing. In China, CAR-T development is booming on basis of ultra-localized clinical centers, thus allowing to support several small start-ups developing CAR-T therapies [2, 9].

China [50] has issued a set of regulations to boost cell and gene therapy, most importantly dual-track approval mechanism for somatic cell therapies, implying that hospitals can legally use somatic-cell therapies through approval by local governments regions, that can be used after a strict inspection, in addition to somatic-cell therapies marketed as a drug from the NMPA. Given that China had set up large number of pilot zones some of which have taken the development of cellular and gene therapies as a high priority, like Hebei, Hainan, Chongqing, and local governments have built industrial parks specialized for cellular therapies including the Zhang-jiang Cell Industrial Park in Shanghai, the China Cell Valley in Nanjing. Several documents of Chinese regulators, like Management of Clinical Research and Transformation Application for Somatic Cell Therapy policy proposed that the somatic cell-based therapies with proven safety and efficacy could be used clinically in selected qualified hospitals under strict supervision. This document declares that the researchers and the project host at these institutions are required to obtain a license from the Chinese regulator, and the somatic-cell therapy Expert Committee will be responsible for evaluation of the licensing process. In this case hospitals even can obtain market authorization for somatic-cell-therapy products, and use the data obtained from clinical research as evidence to support the applications if GCP and GMP practices were followed.

Conclusion

The point-of-care CGT production may be a powerful tool of treating the incurable diseases, providing effective and safe treatment, ensuring broader access and reducing financial burden. Since personalization may interfere with effective commercial models for delivery of such drugs to the market, it opens the non-competitive door for academic institutions to bring such products to the patients. Regulatory pathways for their approval are developing in US, Europe, China, and Russia. POC production of CGT, and, specifically, CAR-T products, has big future not only in cancers, but in other areas, with most promising advances can be seen in treatment of autoimmune diseases. These advancements, if successful, will help crossing the death valley [51] for new CGTs to reach patients all over the world.

Conflict of interests

None declared.

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На пути к персональной генной и клеточной терапии: факторы ускорения и проблемы локальной продукции по месту лечения

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Резюме

Современные достижения в области генной и клеточной терапии показали впечатляющие результаты на протяжении последнего десятилетия, которые привели к разрешению на клиническое использование методик CAR-T-клеточной терапии, что позволяет добиться долгосрочных ремиссий и, в ряде случаев, полного излечения у ранее безнадежных пациентов онкологического профиля. Эти разработки создали возможность для успеха генной терапии, в том числе при таких наследственных заболеваниях, как бета-талассемия и миодистрофия Дюшенна. Однако доступность этих жизненно важных методов терапии все еще очень ограничена ввиду исключительно высокой стоимости и ряда узких мест в персонализованной продукции препаратов. Эффективность персонализированной терапии является проблемой для централизованного производства, которое является обычным для фарминдустрии и регулирующих органов, что может самоограничивать ее развитие. Мы обсуждаем современные доводы в пользу новых перспективных путей клеточной и генной терапии (КГТ), т.е. производства препаратов на месте лечения (POC-продукции) в качестве прогрессивной тенденции их клинического применения. Показано, что POC-продукция на базе академических учреждений может быть одобрена для клинического применения, будучи даже более эффективной, нежели коммерческие продукты, благодаря большей скорости производства, доле качественного продукта и более низких расходах на производство в случае принятия новых регулирующих правил. Примеры успешной POC-продукции для CAR-T-клеточной терапии даже более важны в аспекте новых данных о высокоэффективном внедрении однократной CAR-T-клеточной терапии при аутоиммунных заболеваниях, в том числе системной красной волчанке и тяжелой миастении. После данной терапии отмечены долгосрочные ремиссии, не требующие дополнительного лечения.

Ключевые слова

Клеточная терапия, CAR-T-клетки, стоимость, доступность, регулирование, продукция по месту лечения.