



The CAR T cell revolution: what does it offer, and can we afford it?

In August 2018 the first therapies aimed at re-engineering patients own T cells to attack cancer entered the European market. **Rachel Brazil** looks at how they work, what they achieve, and what the logistical and cost barriers will mean for patients hoping to get access.

In 2012, Emily Whitehead, a six-year-old from Pennsylvania, USA, with chemotherapy resistant acute lymphoblastic leukaemia (ALL) was given an experimental treatment – an infusion of her own

T cells, which had been genetically engineered to attack cancer cells. She was not the first patient to be treated with chimeric antigen receptor (CAR) T cells, but the publicity surrounding her complete remission

hit the headlines in countries across the world: Could this new form of immunotherapy represent a leap into a new era for cancer treatment?

Subsequent clinical trials provided stunning results for several

Cutting Edge

B-cell malignancies, where two or more lines of therapy had failed, particularly in children and young adults (see box opposite). In late 2017 and early 2018 the US regulator, the FDA, approved the first two CAR T-cell therapies – Gilead’s axicabtagene ciloleucel (Yescarta), for adult patients with relapsed or refractory large B-cell lymphoma, and Novartis’s tisagenlecleucel (Kymriah), for patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. The European Medicines Agency (EMA) followed suit in August 2018, also approving Kymriah for use in adults with relapsed or refractory diffuse large B-cell lymphoma, on the basis of results that had become available subsequent to the FDA approval. As a result, the first two CAR T-cell therapies can now be marketed across Europe.

However, as big pharma has moved into the development of CAR T cells, pricing concerns have arisen. Within days of the EMA approval, England’s National Institute for Clinical Excellence (NICE), recommended that Yescarta – priced in the US at \$373,000 – should not be used in the National Health Service, on the grounds of cost-effectiveness. Add to this the drug’s potentially serious side effects, plus the difficulties in manufacturing the cells, and it’s clear that many hurdles have yet to be jumped before this new cell therapy can become widely available.

How it works

Haematologist Michael Schmitt is running several CAR T cell clinical trials at Heidelberg University Hos-

pital, in Germany. He explains that a number of different approaches to CAR T-cell therapy are being explored, which are all designed to take advantage of the human immune system’s ability to kill.

“Inside the donor organism an Armada is built, acting against cancer cells”

T cells are a type of white blood cell that can be armed to recognise and destroy cancer cells via the antigens they display on their surfaces. This can be done by harvesting a patient’s own T cells from their blood, isolating the cells, and then introducing the chimeric antigen into them, which is done by inserting a gene using a viral vector – as if ‘infecting’ the cell with the antigen receptor gene.

This gene then adds the chimeric antigen receptor – a small synthetic protein – to the surface of the T cell, from which location it will be able to recognise a specific marker (known as an antigen) on a cell’s surface. Many different antigens exist on cells, but to date most CARs have been designed to recognise a marker called CD19, which is found on the surface of all B cells (the white blood cells responsible for producing antibodies), including the malignant B cells that cause certain leukaemias and lymphomas.

The modified T cells are then cultured and returned to the patient in a single infusion. This is usually preceded by a course of chemotherapy, designed to deplete the patient’s own immune cells, which helps

the CAR T cells to multiply in the patient’s body. The CAR T cells then fuse to cancer cells with the CD19 marker, which initiates several signalling pathways, leading to elimination of the targeted cancer cell as well as triggering the ‘expansion’ (multiplication) of the CAR T cells.

“Inside the donor organism an Armada is built, acting against cancer cells,” says Schmitt. “You see tumours shrinking, you see billions of leukaemia cells going into apoptosis [cell death].”

Side effects

There’s a catch, however, as CAR T cells can induce serious off-target effects. The intracellular signalling that damages the cancer cells also triggers the release of cytokines – cell-signalling molecules that form a normal part of the immune response system. When present in excess, these cytokines can trigger a huge inflammatory response, known as cytokine release syndrome (CRS). The response is also referred to as a ‘cytokine storm’.

Pere Barba, a haematologist at the Vall d’Hebron Institute of Oncology in Barcelona, describes the impact on the patient. “This is a syndrome that occurs quite early, a few days after infusion, and consists of fever, hypotension, problems breathing, and tachycardia.” Doctors currently use corticosteroids or the rheumatoid arthritis drug tocilizumab to dampen down cytokine release, he says, but stresses that, “Although it’s manageable with medication, in some cases it can be life-threatening.”

There are other side effects, adds Barba, who is currently involved in the first pan-European clinical trial with CAR T-cell therapy for patients

CAR T-cell therapies – the evidence

Childhood ALL

The first CAR T-cell therapy to reach the market was Novartis's Kymriah (tisagenlecleucel). It was approved by the FDA in August 2017 for treating childhood B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in a second relapse, based on the early results of ELIANA, a global phase II trial (American Society of Hematology annual meeting 2016, abstracts #221 and #2801). Complete remission was achieved at three months in 41 out of 50 patients (82%). A 2018 update of 75 patients who had completed three or more months of follow-up showed an overall remission rate of 81%. Remissions were durable, with 80% of those who had achieved remission remaining free from relapse at six months.

Patients did however suffer serious side effects, including cytokine release syndrome, pyrexia, decreased appetite, febrile neutropenia and headache. The most serious side effect was cytokine release syndrome, which occurred in 77% of patients, resulting in admission to intensive care for 35 of them. Neurological events occurred in 40% of patients within eight weeks of infusion; it was grade 3 in 13% of patients, with no instances of grade 4. Kymriah received marketing approval from the EMA in August 2018.

Adult lymphoma

Two CAR T-cell therapies have been approved for use in treating certain adult lymphomas – Novartis's Kymriah and Gilead's Yescarta (axicabtagene ciloleucel).

Kymriah gained approval for use in adults with relapsed or refractory diffuse large B-cell lymphoma, on the basis of the JULIET trial, which showed an overall response rate of 52% among 93 evaluable patients,

with a complete response in 40% and partial response in 12% (European Hematology Association annual meeting 2018, abstract #S799). Among those reaching complete response, 83% remained in complete response at 12 months. Patients had a 65% chance of being relapse-free one year after onset of response. Cytokine release syndrome grade 3/4 was recorded in 22% of patients, and grade 3/4 neurologic adverse events in 12%. Grade 3/4 cytopenia lasting more than 28 days, grade 3/4 infections, and grade 3/4 febrile neutropenia occurred in 32%, 20% and 15% of patients, respectively. Approval for this indication was given by the FDA in May 2018, and by the EMA in August 2018.

Approval of Gilead's **Yescarta** for patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease was based on the pivotal phase II ZUMA-1 trial (*NEJM* 2017, 377:2531-44). Among the 111 patients who were enrolled, axicabtagene ciloleucel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was 54%. With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. The most common adverse events of grade 3 or higher during treatment were neutropenia (in 78% of the patients), anaemia (in 43%), and thrombocytopenia (in 38%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively.

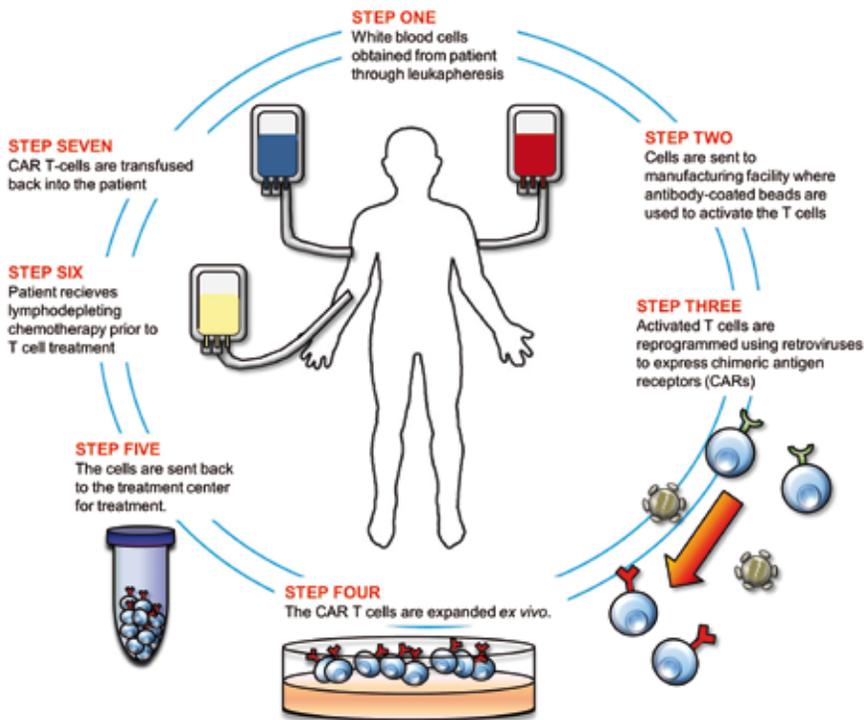
Yescarta was approved by the FDA in October 2017, and by the EMA in August 2018.

with aggressive B-cell non-Hodgkin lymphoma. "It's not very well understood, but patients can have a large variety of neurological symptoms including seizures, speaking problems, confusion, and dizziness, and this tends to come seven to ten days after CAR T infusion." He also mentions longer term risks of infection, as patients will have been immunosuppressed.

Toxic side effects, principally connected to cytokine release syndrome, have led to the deaths of between three and four out of every hundred patients in trials so far. One precaution could be to design 'kill switches' into the CAR T cells so their effects can be controlled. This is an approach being developed by Collectis, a French biotech spin-out from the Institut Pasteur, which is now devel-

oping its own CAR T-cell therapies in collaboration with the pharmaceutical company Servier. "We have been adding two genes: one to be able to recognise the cancer cell and one additional gene to be able to eliminate the [CAR T] cells if needed," says Laurent Poirot, head of early discovery at Collectis. The second, 'kill switch', gene produces a receptor embedded into the CAR molecule on

How it's done



A patient's T cells are harvested through leukapheresis, followed by T cell activation on antibody-coated beads (which act as artificial dendritic cells). The activated T cells are transduced with a construct encoding the chimeric antigen receptor (CAR). These reprogrammed CAR T cells are culture expanded and subjected to quality control testing prior to cryopreservation for transport of cells to the treatment facility. Prior to CAR T cell infusion, the patient receives chemotherapy to deplete native lymphocytes that can decrease efficacy of the infused cells

Source: Debbie King (2017). FDA Approves First CAR T-Cell Therapy - The evolution of CAR T-Cell Therapy. (CAR T Cell Therapy Workflow) Retrieved from <https://cellculturedish.com/fda-approves-first-car-t-cell-therapy-the-evolution-of-car-t-cell-therapy/>

the surface of the T cells. If a patient suffers dangerous levels of toxic side effects, a monoclonal antibody drug, rituximab, can be injected. It will bind to the 'kill switch' receptor and trigger cell signalling that leads the patient's own immune system to kill the CAR T cells.

Houston-based Bellicum Pharmaceuticals have also developed a 'kill switch', which uses the small-molecule drug rimiducid to set it off.

The CAR T cells are engineered with two proteins that combine in the presence of rimiducid, and this activates an enzyme that precipitates cell death.

CAR T in Europe - the roll out

The task of rolling out CAR T-cell therapy across Europe poses a number of logistical issues, as Zack

Pemberton-Whiteley, who chairs the Acute Leukemia Advocates Network, explains. "It isn't a tablet where you can just start handing it over," he says, "there is lots of commissioning that needs to be in place, so it's an unusual situation." One hurdle is the manufacturing of the CAR T cells, which need a facility with GMP (Good Manufacturing Practice) certification as well as a licence to handle genetically modified organisms (GMOs).

Currently Novartis and Gilead are manufacturing their CAR T-cell products in the US, shipping patients' cells in and out of centralised facilities. Novartis is also collaborating with the Leipzig-based Fraunhofer Institute to manufacture CAR T cells for European clinical trials. The companies intend to continue these arrangements initially, but both have announced plans to build their own European facilities. In July 2018, Novartis announced a partnership with French manufacturer Cell for Cure, based in Les Ulis, near Paris, which is set to open in 2019; Gilead are developing a site in the Netherlands.

Currently CAR T-cell therapy takes a minimum of 18 days from removal of a patients cells to infusing the modified and expanded cells back into the patient. Most producers are now freezing the modified cells to allow the infusion to be delayed, if that should be required on the grounds of the patient's health or any other reason.

The complex logistics involved have opened up a specialist niche in the health technology market that is spawning companies such as TrakCel, which helps with collation, tracking and documentation involved in cell and gene therapy. Founded in Cardiff, Wales, in 2012, it is now expanding into the US market.

“There is a real challenge just around ensuring the chain of identity for each individual [patient’s cells] and being able to maintain from a regulatory perspective all the correct documentation and records that are required,” says Matthew Lakelin, TrakCel’s Chief Scientific Officer. The task is not just ensuring the right cells are given to a patient, but making sure the right facilities and personnel are available to administer the therapy and deal with the side effects. “It becomes a little bit of a headache as you add more and more patients and more and more clinical sites,” he says.

As a consequence, argues Lakelin, treatment in Europe is likely to be restricted to a small number of clinical centres to which patients will need to travel. “It’s almost going to be similar to how kidney dialysis started, in very specialist units with trained physicians. They then moved dialysis into smaller hospitals and eventually into cottage [local] hospitals. So I think you will see a spread of these products over the next ten years, and they will become more commonplace.”

CAR T cell manufacturers are also dealing with a fairly complicated regulatory landscape in Europe, which is overseen by the EMA Committee for Advanced Therapies. The modified CAR T cells themselves are considered as Gene Therapy Medicinal Products but, as Lakelin explains, the starting material – i.e. the patient’s own cells – are governed by transplant and blood product legislation, “so there is no [single] existing pathway through from a regulatory perspective.” On top of this, the final CAR T cells are classed as genetically modified organisms (GMOs), which are regulated differently by each European country.

“It’s not just about giving the right cells to a patient, but having the right facilities and personnel available to administer the therapy and deal with the side effects”

It’s complicated admits Martina Schübler-Lenz, who is deputy head of the Advanced Therapy Medicinal Products section at the Paul Ehrlich Institute, in Langen, Germany, and chairs the EMA’s Committee for Advanced Therapies. But the EMA has a framework for dealing with advanced therapies, she says, and “new regulations are currently not needed.”

Putting a price on CAR T cells

With two CAR T-cell therapies now approved, the focus is moving to pricing, and the fear that high costs will limit patient access. Even though European prices are likely to be less than those in the US, price will still be a huge issue. Reimbursement is negotiated by individual European countries, and the picture so far looks mixed. In Germany, Novartis has set a list price of €320,000 (\$371,000), which will be subject to the usual negotiations and cost-benefit assessments with insurers. In the UK, NICE made a speedy agree-

ment with Novartis to green-light Kymriah at £282,000 (\$361,000), for children and adults with refractory or relapsed B-cell ALL – less than the \$475,000 price listed in the US. Yescarta did not fare so well, although Gilead will get a chance to present further data on clinical and cost-effectiveness.

In a report published in June 2018 – *CAR-T Cell Therapies: How much for survival?* – the Access to Medicines Task Force of the Association of European Cancer Leagues (ECL) argue that, even if they are effective, the high price would be unsustainable in Europe. “It will be a challenge (if not impossible) for European payers to ensure access to the CAR-T-cell therapies for all patients under the current functioning of healthcare systems,” they conclude (bit.ly/ECL_CAR-T_cost).

Šarunas Narbutas, president of POLA (Lithuanian Cancer Patient Coalition), who has campaigned for the introduction of modern, effective leukaemia treatment in Lithuania, agrees. “I am pretty confident that there won’t be any hospitals in Lithuania which will be receiving CAR T therapy patients,” he says.

He hopes, however, that companies may agree to patient access and compassionate use schemes, particularly as many of those eligible will be children. “[In Lithuania], I am aware that there are currently over 60 [access] agreements in place with industry regarding products,” says Narbutas. He adds though that, given the extensive infrastructure required for CAR T-cell therapy, this will not be simple and may require a close working relationship with a clinical centre in another part of Europe.

Schmitt, who is running a number of CAR T clinical trials, argues that

The pricing controversy

The Access to Medicines Task Force of the Association of European Cancer Leagues (ECL) has suggested the debate on CAR T cell pricing represents the current debate on drug pricing models and a push towards 'value-based' drug pricing (bit.ly/ECL_CAR-T_cost). A value- or outcome-based pricing model suggests that, rather than relating price to development costs, a drug's price should relate to the benefit it provides. For example, it has been reported that in the US Novartis had briefly suggested (and quickly dropped) a plan to only charge for Kymriah where patients responded in the first month.

The value-based model has many supporters, but "the problem with this is that [the idea] has become hijacked to justify the price [pharma] want to charge," says Anna Prokupkova, Policy & Project Officer at the ECL, and a co-author of the Task Force report '*CAR-T cell therapies: How much for survival?*' There still needs to be some basic agreement on what constitutes a fair price, even for a medicine that may save children's lives, she argues. Pharma argue that high prices represent the high research and development costs for novel technologies such as CAR T-cell therapy. Novartis have said they spent more than \$1 billion since 2012 on bringing Kymriah to market (bit.ly/Forbes-CAR-T_cost). 'We do think that we should award innovation, but there has to be some sort of a scale where you can actually measure this,' says Prokupkova.

And as she points out, in the case of CAR T-cell therapies, that innovation was funded in part by public research money – which has been estimated at around \$200 million in the US alone. This should be taken into account, she argues, so tax payers do not end up paying twice. But Joseph Jimenez, Novartis's CEO, has said their spending "dwarfs anything the government has invested through NIH grants."

In a blogpost published by the health policy journal *Health Affairs*, David Mitchell, co-founder of the US advocacy group Patients for Affordable Drugs, estimated that "Novartis could cover both its historic margins and continuing research and development spending at a retail price [for Kymriah] of \$160,000," rather than the \$475,000 current US price tag for Kymriah (bit.ly/Mitchell_CAR-T_cost).

Obviously there are many arguments to be made over the exact costs; for instance, Mitchell uses a value of \$40,000 for the cost of manufacturing CAR T cells per patient, while Novartis have said the true figure is much larger, although they have been unwilling to provide details (bit.ly/Forbes_CAR-T_cost).

Yet even at \$160,000, Kymriah will still be unaffordable in some parts of Europe. "In (many eastern European) countries, they don't even have the basic immunotherapies, so their access to CAR T can be absolutely forgotten for now," says Prokupkova.

price will be crucial in determining whether the new therapy will be used in more than a small subset of refractory patients. "What needs to be proven is that, in the long run, CAR T-cell therapy is really superior over allogeneic transplantation, which is almost a give-away compared to the price of CAR T-cell therapy – only 20% of the costs," he says.

But making these types of decision is very hard without long-term data. "We say this is a potentially curative therapy, but actually we don't have any patients who have been on it beyond 15 years," says Pemberton-Whiteley. In February 2018 the EMA held a workshop on how to col-

lect such long-term real-world data (bit.ly/EMA_CAR-T_workshop), and the Agency is committed to supporting existing registries and establishing a centralised process for obtaining data.

Where next for CAR T-cell therapies?

The extraordinary results with blood cancers has spurred interest in CAR T-cell therapies for solid cancers. "If you go to breast cancer, colorectal cancer, or prostate cancers – the big killer diseases – there was much hope, but this has not been

proven in animal models so far," says Schmitt. In the blood, cancer cells can be flooded with CAR T cells, he explains, but many solid tumours have few blood vessels at their centres and T cells are therefore unable to reach their targets. Tumours also create their own barriers: "You have something like a fence – a cluster of cells around tumours that are like an armour suit and defend the tumour against T cell attacks."

There are examples of success, however. Researchers at Baylor College of Medicine in Houston produced CAR T cells that respond to antigens on glioblastoma (brain cancer) cells. The first trials have

established safety as well as promising efficacy (*JAMA Oncol* 2017, 3:1094–101). The French biotech, Cellectis has also been trying to tackle the problem; they have generated CAR T cells that are active only in the sort of hypoxic environment that is characteristic of solid tumours.

Allogeneic CAR T cell therapy uses donor cells, avoiding the high costs, and the delays, involved in genetically engineering each patient's cells separately

Cellectis are also pioneers in the field of allogeneic, or universal – ‘off-the-shelf’ – CAR T cells. This therapy uses donor cells, avoiding the high costs, and the delays, involved in harvesting and genetically engineering each patient's cells separately. The challenge here is how to overcome the problem of graft-versus-host disease – a serious complication that can occur with cell transplants. “Anytime you inject a foreign body into a person it can be rejected, but also the foreign cell can attack,” explains Stéphane Depil, executive vice president of research and development at Cellectis. The patient suffers skin rashes, intestinal inflammation and liver problems, and these can be fatal, he says.

Origins of CAR T-cell therapy

The origins of CAR T-cell therapy can be traced back to observations made in the 1980s that infusing relapsed leukaemia or lymphoma patients with donor T cells (or T lymphocytes) alongside stem cell transplants could be beneficial. In 1989, Zelig Eshhar at the Weizmann Institute of Science came up with the idea of engineering a T cell that could target and kill cells (*Proc Natl Acad Sci USA* 86:10024–28). Over the next 20 years, researchers developed the approach, including Carl June at the University of Pennsylvania who treated the first patient with so-called CAR T cells in 2010 (*Cancer Res* 2010, 70:9053–61).

By 2012 the pharmaceutical industry had jumped on board, with Novartis partnering with the University of Pennsylvania to develop and commercialise CAR T-cell therapies. The potential for the treatment fuelled multi-billion-dollar acquisitions – Gilead acquired the small, Santa Monica-based, biotech KITE for \$11.9bn in 2017, and in 2018 Seattle-based Juno therapeutics was acquired by the US biotech Celgene for \$9bn. Other companies joining the field are Pfizer, who have licenced technology from Cellectis, GSK working with Philadelphia-based Adaptimmune, and Johnson & Johnson, partnering with China's Legend Biotech.

Despite this, in 2011 Cellectis took a bet on allogeneic approaches and started using gene editing to make donor CAR T cells compatible with anyone. They knew certain cell receptors are responsible for graft-versus-host disease, by allowing T cells to discriminate between self and non-self. “Our strategy was to inactivate specifically those genes in the CAR T cells so that, while we are providing them with a receptor that can redirect them to cancer cells, we are removing the receptor that allows them to recognise non-self cells and attack the patient,” explains Depil.

Their CAR T cell, UCART19, met early success at Great Ormond Street Hospital, London, in 2015, putting two children with ALL into molecular remission, which persisted until conditioning ahead of successful allogeneic stem cell transplantation (*Sci Transl Med* 2017, 9(374): eaaj2013). Cellectis now has two candidates in clinical trials,

and in April entered a partnership with Pfizer to further develop their CAR T-cell therapies. Several other companies are developing similar strategies, including San Francisco-based Allogene Therapeutics, Belgian biotech Celyad and Massachusetts-based Crispr Therapeutics.

As TrakCell's Lakelin points out, whether or not allogeneic CAR T cells turn out to be the next step in cell therapy, right now “industry and clinicians are going to have to get used to the context and cycles of the autologous CAR T cell.” CAR T-cell therapies could be the start a whole new era of cancer treatment. And ironically, in an era where everybody is talking about patient-centred medicine, says advocate Pemberton-Whitely, “CAR T is one of those examples that really brings it home, because the medicine wouldn't exist without the patient!”

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