On 5 September 2018, NHS England announced that “children and young people in England will receive a ground-breaking cancer treatment, the first in what is expected to be a rapidly expanding class of personalised cancer treatments available on the NHS”. The new treatment was tisagenlecleucel (Kymriah), one of two newly-licensed chimeric anti-gen receptor (CAR)-T cell therapies. NHS England described CAR-T cell therapy as a “true game changer” and “the most exciting advance in treatment for childhood leukaemia”. Manufacturer Novartis described its product as “a transformational milestone”. But excitement at the news was tempered by acceptance that the cost of this “immensely complex” treatment is high (£282,000 per person, undiscounted), awareness of the potential for serious toxicity and that relatively few patients would, at this stage, be offered treatment.

Another CAR-T cell therapy, axicabtagene ciloleucel (Yescarta), has fared less well so far: manufacturer Gilead Sciences has not reached a pricing agreement with NICE, which is now consulting on its proposals not to recommend it for NHS use within its marketing authorisation because it is so expensive, nor to include it in the Cancer Drugs Fund.

What is CAR-T therapy?
This approach to cancer therapy has been evolving for approximately 15 years. It is a method of modifying a person’s T cells to express receptors for a target antigen – in this case CD19, a protein that is expressed by healthy and malignant B cells. A viral vector is used to introduce into human T cells the gene that codes for the receptor, which is then expressed on the cell membrane. The receptor, a fragment of a mouse antibody that binds to human CD19, is termed ‘chimeric’ because it is derived from another species and expressed by human cells.

This strategy generates T cells that

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**Figure 1. How CAR-T cell therapy works**

1. T cells harvested from patient’s blood
2. T cells treated with viral vector to express receptors for a target antigen (CD19)
3. CAR-T cells expanded and infused back into the patient
4. CAR-T cells recognise and bind to CD19 expressed on malignant B cells, activating an immune response against them
can recognise a tumour-associated antigen and bind to it, activating the person’s immune response against the tumour cell.\textsuperscript{5} There have been three generations of chimeric antigen receptors to date, the third (current) generation having the greatest T cell signalling capacity, leading to an enhanced immune response.\textsuperscript{6}

CAR-T cell therapy is perhaps the ultimate in personalised medicine. The patient’s T cells are harvested, treated with the viral vector and expanded in the laboratory; a process that takes three to four weeks. The modified cells are then infused back into the patient over about 30 minutes (see Figure 1). A CAR-T cell therapy is therefore not a single molecule but a preparation of patient-specific engineered T cells, given as a one-off treatment.

Two CAR-T cell therapies were approved in Europe in 2018, tisagenlecleucel and axicabtagene ciloleucel; their licensed indications and instructions for use are summarised in Table 1. Before treatment, the patient must undergo lymphodepleting chemotherapy; premedication with paracetamol and an antihistamine should be given and the anti-IL-6 receptor monoclonal antibody tocilizumab must be available to treat serious toxicity. CAR-T therapy may only be provided by an accredited centre; the first three in England are in Newcastle, Manchester and London.

### Efficacy in clinical trials
Evidence for the efficacy of CAR-T cell therapy comes from non-comparative phase 2 trials in patients who had refractory disease after several lines of treatment or for whom standard treatment was unsuitable.

Axicabtagene ciloleucel was evaluated in the ZUMA-1 study,\textsuperscript{7} in which it was administered to 101 patients with refractory lymphoma (diffuse large B cell lymphoma, primary mediastinal B cell lymphoma or transformed follicular lymphoma). The primary endpoint was the combined rates of complete and partial responses. Contrary to UK practice, some patients received a second treatment if they initially responded but their disease progressed after three months. Most patients (median age 58 years, range 23–76) had advanced disease, which in 77% of cases was resistant to second-line or later therapies.

After a minimum six months’ follow-up (n=92), the combined response rate was 82% (compared with the historical response rate to traditional salvage therapy of 20%), with a complete response in 54% of patients. The median time to response was one month (range 0.8–6.0) and the median duration of response was 8.1 months. Response rates were similar across patient subgroups and different types of lymphoma.

A second analysis after at least one year’s follow-up (n=101) showed the objective response rate was still 82% and the complete response rate was now 58%. In 23 patients, a complete response did not occur until 15 months after treatment. The median duration of response was 11.1 months. Rates of progression-free survival were 49%, 44% and 41% at 6, 12 and 15 months respectively. Overall survival at the same time intervals was 78%, 59% and 52%.

### Table 1. Indications and use of the CAR-T cell therapies tisagenlecleucel and axicabtagene ciloleucel

<table>
<thead>
<tr>
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<th>Tisagenlecleucel</th>
<th>Axicabtagene ciloleucel</th>
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<tr>
<td><strong>Licensed indications</strong></td>
<td>Children and young adults up to 25 years of age with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse Adults with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after two or more lines of systemic therapy</td>
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<td><strong>Dose</strong></td>
<td>B cell ALL: ≤50kg: 0.2–5 x 10^8 CAR-positive viable T cells/kg body weight &gt;50kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells DLBCL: 0.6–6 x 10^8 CAR-positive viable T cells 2 x 10^6 CAR-positive viable T cells per kg (or maximum of 2 x 10^8 CAR-positive viable T cells for patients ≥100kg)</td>
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<td><strong>Lymphodepletion</strong></td>
<td>B cell ALL: fludarabine/cyclophosphamide (alternative is cytarabine/etoposide) DLBCL: fludarabine/cyclophosphamide (alternative is bendamustine)</td>
<td>Fludarabine/cyclophosphamide</td>
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<tr>
<td><strong>Premedication</strong></td>
<td>Paracetamol, diphenhydramine</td>
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<td><strong>Monitoring for toxicity</strong></td>
<td>Preferably in hospital for 10 days then patients advised to have ready access to medical help for four weeks</td>
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<tr>
<td><strong>Contraindications</strong></td>
<td>Hypersensitivity to components of the preparation Contraindications to lymphodepleting therapy</td>
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For tisagenlecleucel, the pivotal study in patients with relapsed or refractory B cell acute lymphoblastic leukaemia included the treatment of 75 children and young adults. Their median age was 11 years (range 3–23) and they had previously received a median of three therapies (range 1–8); 61% had previously undergone allogeneic stem cell transplantation. The primary endpoint was overall remission rate (defined as complete remission, or complete remission without complete haematological recovery within three months). Median duration of follow up was 13.1 months (minimum three months).

The overall remission rate after three months was 81%. The authors note that the response rate with established treatments is currently 20%–40%. Complete remission occurred in 60% of patients, of whom 95% had no residual disease by day 28. Relapse-free survival among responding patients was 80% at six months and 59% at 12 months, and overall survival was 90% at six months and 76% at 12 months.

The pivotal study of tisagenlecleucel in adults with relapsed or refractory diffuse large B cell lymphoma has not been published in full. It included 99 patients (median 56 years, range 22–76) whose disease had progressed after receiving two or more lines of chemotherapy and for whom autologous stem cell transplant was unsuitable or had failed. They had received a median of three previous therapies (range 1–6) and 47% had undergone stem cell transplantation.

In 81 patients (at least three months follow-up or earlier discontinuation), the overall response rate to tisagenlecleucel treatment was 53% (with a 40% complete response). In 46 patients who could be evaluated after six months, the complete response rate was 30% and the partial response rate was 7%. The six-month probability of being relapse-free was 74% and that of overall survival was 65% (95% CI 51.5–74.8%). No patient with a partial or complete response subsequently underwent stem cell transplantation.

Adverse effects
Clinical trials of CAR-T cell therapy for the licensed indications reveal a heavy burden of toxicity. Adverse event rates differed in these trials but it is not possible to infer that one treatment is safer than the other because the patient populations were dissimilar. CAR-T cell therapy may be associated with adverse effects due to depletion of B cells, cross-reactivity with other cell proteins, anaphylaxis and tumour lysis syndrome, but the most prominent adverse effect is cytokine-release syndrome (CRS). CRS is a systemic inflammatory syndrome that has also been reported after treatment with monoclonal antibodies and non-biological chemotherapy but it has emerged as one of the most frequent complications of CAR-T cell therapy due to the massive release of a range of cytokines following activation of bystander immune and other cells. Symptoms range from mild flu-like illness to severe, life-threatening multiple-organ failure. CAR-T cell therapy may also be associated with neurological toxicity ranging in severity from headaches, confusion and altered consciousness to hallucinations, dysphasia, movement disorders (eg ataxia, apraxia, facial nerve palsy, tremor, dysmetria) and seizures.

Higher risk of CRS and more severe CRS is associated with greater disease burden at first treatment, CAR-T cell dose, young age, extent of T cell activation and more pronounced lymphodepletion. It is therefore possible that different cancer types are associated with different risks of CRS. Frequent adverse haematological events include increased white cells, platelets and haemoglobin.

Treatment with tocilizumab improves most of the signs and symptoms of CRS within hours, though several doses may be needed if the response is partial or relapse occurs, and shock may not resolve for several days. Patients who need multiple doses of tocilizumab have also received adjunctive treatment with corticosteroids. This does not affect the efficacy of CAR-T cell therapy because T cell expansion continues after treatment with tocilizumab and corticosteroids.

All patients treated with axicabtagene ciloleucel in the ZUMA-1 study experienced an adverse event, which was at least severe in 95%. CRS occurred in 93% of patients and was at least severe in 13%. Common symptoms were pyrexia, hypoxia and hypotension. The median time after infusion to onset of CRS was two days (range 1–12) and the median time to resolution was eight days. Two patients died of complications of CRS but signs and symptoms resolved in all survivors. An adverse neurological event was experienced in 64% of patients, which was at least severe in 28%, most often involving encephalopathy, confusion, aphasia or somnolence. The median time to onset of a neurological event was five days (range 1–17) with median resolution on day 17 after infusion.

In children and young people with B cell lymphoblastic leukaemia treated with tisagenlecleucel, 95% experienced a treatment-related adverse event which was at least severe in 73%. CRS occurred in 77% (and was at least severe in 46%) with a median time to onset of three days (range 1–22) and a median duration of eight days (1–36). A total of 47% were admitted to intensive care for management of CRS. One patient died within 30 days of infusion from cerebral haemorrhage following CRS. Neurological events occurred in 40% of patients (severe in 13%) within eight weeks after infusion, more often in those with CRS and more severely with worse CRS. The most frequent neurological events were encephalopathy, confusion, delirium, tremor, agitation and somnolence. One patient died of encephalitis in association with prolonged neutropenia and lymphopenia.

The details available for the treatment of adults with diffuse large B cell lymphoma also reveal a high rate of adverse events. At least severe adverse events affected 86% of patients, with CRS in 58% (at least severe in 23%). At least severe neurological adverse events occurred in 12% of patients. No deaths were attributed to tisagenlecleucel.

Other applications of CAR-T cell therapy
The principle of engineering T cells to target specific proteins is generally applicable and it is reported that CAR-T cell therapies against over 25 cancer biomarkers are now being evaluated in more than 100 trials. However, the
response of solid tumours has been disappointing and CAR-T cell therapy will need further refinement to enhance its effectiveness.\textsuperscript{13} Tisagenlecleucel is now undergoing clinical trials in the treatment of Hodgkin and non-Hodgkin lymphoma, multiple myeloma and pancreatic cancer, including combinations with other anti-cancer drugs. Axicabtagene ciloleucel is also undergoing trials as a treatment for non-Hodgkin lymphoma.

Place in therapy
NICE has now published a final appraisal determination recommending tisagenlecleucel for use within the Cancer Drugs Fund for the treatment of relapsed or refractory B cell acute lymphoblastic leukaemia in young people (up to the age of 25 years), if the conditions of the pricing agreement are met.\textsuperscript{14} NICE estimates that between 25 and 30 people per year will meet the eligibility criteria in England. NICE is also working on a technology appraisal of tisagenlecleucel for its use in adults with relapsed or refractory diffuse large B cell lymphoma after two or more systemic therapies, but did not recommend it for this indication in its initial appraisal consultation document.

The future for axicabtagene ciloleucel in the UK looks less certain unless a price acceptable to the NHS can be agreed. In NICE’s initial appraisal consultation document on its use within its marketing authorisation, ie adults with relapsed or refractory diffuse large B cell lymphoma or primary mediastinal large B cell lymphoma after two or more systemic therapies, it did not recommend the therapy because the cost estimates are above the range normally considered to be a cost-effective use of NHS resources.

Conclusion
CAR-T cell therapy is a radical approach to cancer treatment that, according to the follow-up available so far, offers a substantial improvement in outlook for people who have exhausted conventional treatment options and now have a poor prognosis. It is too soon to talk of a cure for some patients and the hype that characterised NHS England’s funding announcement seems over-optimistic for the majority of people with cancer.

The CAR-T cell developments introduced in 2018 are probably the tip of the iceberg, both in terms of indications and preparations, though there is clearly progress to be made in the treatment of solid tumours. CAR-T cell therapy is associated with frequent and serious toxicity. This can usually be effectively managed but it has proved fatal in a small number of cases. Finally, the highly personalised nature of this treatment strategy means it is likely to remain relatively expensive, suggesting that for some time its use may be limited to children and young people, and to patients who have exhausted other options.

References

Declaration of interests
None to declare.

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