# CAR T-cell therapy: perceived need versus actual evidence

September, 2018, witnessed two advances with chimeric antigen receptor (CAR) T-cell therapy for patients with haematological malignancies, albeit accompanied by contradictory access recommendations for the UK National Health Service (NHS). On the one hand, draft guidelines by the UK National Institute for Health and Care Excellence (NICE) did not recommend the use of axicabtagene ciloleucel (Kite Pharma/Gilead) for various types of B-cell lymphoma in adults, a decision contrary to the approval of the drug in the EU and by the US Food and Drug Administration. On the other hand, NHS England (in lieu of a formal NICE recommendation) struck a clandestine deal with Novartis via the Cancer Drugs Fund to pay for tisagenlecleucel for children and young adults with B-cell acute lymphoblastic leukaemia. The deal, agreed less than 10 days after the European approval of the drug, means that patients in England could be the first in Europe to gain access to the treatment—a remarkable prospect for the beleaguered NHS. However, does CAR T-cell therapy represent a major clinical advance justifying the excitement and the extra cost, or is this another case of hype and overpromise?

The main issue regarding these decisions is whether CAR T-cell therapy is more effective than current standard of care—and therein lies a problem. There are no prospective, head-to-head comparisons with existing care. Currently, CAR T-cell therapy is only considered in experimental settings after exhausting all other treatment options and is thus used as a treatment of last resort, limiting the available evidence. In the UK, only 200 of about 5000 people diagnosed each year with diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma might be eligible for CAR T-cell therapy, and only 15–20 of 400 children each year with acute lymphoblastic leukaemia. The current evidence for axicabtagene ciloleucel is from a phase 2 trial of 101 patients with refractory disease, which showed an objective response of 82%. For tisagenlecleucel, a non-comparative, phase 1–2 trial of 75 patients, reported a remission within 3 months of 81%. Taken alone, these results seem promising, but the lack of control group in both trials and the choice of surrogate primary endpoints make the benefits difficult to discern. Additionally, the side-effects of immunotherapy can overshadow clinical benefits, and CAR T-cell therapy is proving to be particularly challenging: for example, 95% of patients treated with axicabtagene ciloleucel had adverse events of grade 3 or worse, including haematological and neurological toxicities. Thus, long-term follow-up data on the safety of these therapies are essential.

It is within this context that the excitement surrounding CAR T-cell therapy is balanced against the reality of another case of false hope. Many patients might feel that they are missing out on a new wonder drug, a feeling that might be further exacerbated by international differences in eligibility criteria; for example, the threshold of minimally residual disease at which a child is eligible for CAR T-cell therapy is more liberal in the USA than in the UK. But these differences are misleading and are a consequence of the scant clinical evidence available currently, and the subjective nature of clinical decision making for these specific treatments.

The key driver of the NICE and NHS England decisions has been cost. Axicabtagene ciloleucel is believed to cost more than £50 000 per quality-adjusted life-year (QALY) gained, which is at the upper limit of tolerance for cancer treatments. The manufacturer has proposed a commercial arrangement that might sway the eventual decision in favour of approval, although at the time of writing, NICE has requested the manufacturer find more UK data from which a comparison with the current standard of care can be made. Tisagenlecleucel, by contrast, which is presumably costing less than the £282 000 list price in the arrangement secured by NHS England, might have a more favourable cost per QALY because children have a longer life expectancy than older patients, provided toxicities are manageable and not debilitating.

The recent announcements on the effectiveness and availability of CAR-T cell therapy in the UK are bittersweet. Potentially tremendous medical advances tempered by many unknowns. Ultimately, more robust evidence is needed to be able to make appropriate decisions, but the high prices set by pharmaceutical companies do make it difficult for universal health-care systems to justify cost-effectiveness and treatment availability. Results from ongoing studies are eagerly awaited to better elucidate the fate of these latest developments in the immunotherapy revolution.

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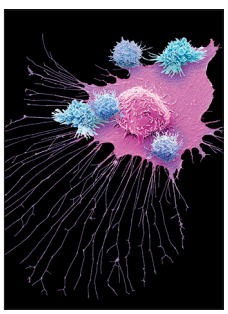

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For more on **NHS England's statement on the approval of for children** see https://www.england.nhs.uk/2018/09/nhs-england-announces-groundbreaking-new-personalised-therapy-for-children-with-cancer/

For more on **axicabtagene ciloleucel in adults** see *N Engl J Med* 2017; **377:** 2531–2544

For more on **tisagenlecleucel in children and young adults** see *N Engl J Med* 2018; **378:** 439–448