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Review Article

CAR T-Cell Therapy Outcomes and Toxicity Profiles in Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

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Summary

CD19-directed CAR T-cell therapy induces remission in around four out of five children with relapsed or refractory B-cell leukaemia, all of them residual disease negative. Two years later, roughly a third have relapsed or died. The problem in this disease has moved from achieving remission to keeping it.

Objectives: To review the published evidence on CD19-directed CAR T-cell therapy in relapsed or refractory B-cell acute lymphoblastic leukaemia: what remission rates are achieved, how durable those remissions are, what toxicities occur and at what severity, and why the available products are difficult to compare.

Material and Methods: Narrative review of registration trials, extended follow-up analyses, registry cohorts and toxicity grading consensus documents indexed in PubMed and the major haematology journals. Studies were eligible if they reported efficacy or toxicity outcomes for CD19-directed CAR T-cell therapy in a defined B-cell acute lymphoblastic leukaemia population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: In the paediatric and young adult registration trial, overall remission within three months was 81 per cent among 75 evaluable infused patients, and every responder was residual disease negative by flow cytometry. Relapse-free survival at 18 months was 66 per cent (95% CI 52-77) and overall survival 70 per cent (95% CI 58-79), falling to 63 per cent at three years with a remission rate of 82 per cent on extended follow-up. Cytokine release syndrome affected 77 per cent of patients with 48 per cent grade 3 or 4 on the Penn scale, all reversible, and grade 3 neurological events occurred in 13 per cent. Of 25 post-infusion deaths, 2 occurred within 30 days and 23 later. In the adult trial, 55 infused patients achieved 71 per cent remission with durable remission in 48 per cent at one year, and grade 3 to 4 cytokine release syndrome and neurotoxicity occurred in 24 and 25 per cent respectively.

Conclusion: Remission rates are high and residual disease negativity near universal among responders, but a third of patients are dead within three years and most deaths occur well beyond the acute toxicity window. The two licensed products were graded on different scales, so their toxicity figures cannot be compared directly.

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, B-ALL – B-Cell Acute Lymphoblastic Leukaemia, CAR – Chimeric Antigen Receptor, R/R – Relapsed or Refractory, CRS – Cytokine Release Syndrome, ICANS – Immune Effector Cell-Associated Neurotoxicity Syndrome, ORR – Overall Remission Rate, MRD – Minimal Residual Disease, RFS – Relapse-Free Survival, OS – Overall Survival, HSCT – Haematopoietic Stem Cell Transplantation, scFv – Single-Chain Variable Fragment.

Keywords: Acute Lymphoblastic Leukaemia; CAR T-Cell Therapy; Cytokine Release Syndrome; Neurotoxicity; Relapsed Refractory Disease

Introduction

Relapsed or refractory B-cell acute lymphoblastic leukaemia had a poor outlook with conventional salvage, and repeated intensive chemotherapy in a heavily pretreated patient rarely produced durable benefit [1,2]. CD19-directed chimeric antigen receptor T cells changed that, taking autologous T cells, transducing them to express a receptor recognising CD19, and reinfusing them after lymphodepletion [3,4].

Two products are licensed for this indication and they differ in design and in target population. One uses a 4-1BB costimulatory domain and is approved for patients aged 25 and under in second or later relapse; the other uses a CD28 domain and is approved for adults from 18 years, including first relapse [5,6,7]. A third product entered use more recently [8].

Both produce remission rates that would have been implausible a decade ago in this population, and both carry toxicities that are specific to the modality rather than shared with chemotherapy: cytokine release syndrome and neurological events driven by immune activation rather than cytotoxicity [9,10].

This review sets out what remission rates and durability the trials achieved, what toxicity was observed and how it was graded, when deaths occur relative to infusion, and why the products resist direct comparison.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of CAR T-cell therapy in B-cell acute lymphoblastic leukaemia. Search terms combined chimeric antigen receptor, CD19, tisagenlecleucel and brexucabtagene with acute lymphoblastic leukaemia, relapsed, refractory, cytokine release syndrome, neurotoxicity and durability. Reference lists of retrieved trials and consensus documents were screened by hand.

Eligibility: Studies were included if they reported efficacy or toxicity outcomes for CD19-directed CAR T-cell therapy in a defined B-cell acute lymphoblastic leukaemia population, or established toxicity grading criteria. Trials in lymphoma are cited only where they establish the modality or the grading approach, and are identified as such.

Data extraction and handling: Design, cohort size, product, age range, follow-up duration, toxicity grading scale and reported outcomes were extracted as published. The grading scale is stated alongside every toxicity figure, because the products were assessed on different scales and the resulting percentages are not interchangeable. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

Remission rates are high and deep: The registration trial for the paediatric and young adult product enrolled patients aged 3 years and above at screening and 21 or under at diagnosis, with at least 5 per cent marrow blasts, across 25 centres. Among 75 infused patients evaluable for efficacy, overall remission within three months was 81 per cent, and every patient who responded was negative for minimal

residual disease by flow cytometry [5,11].

That combination is unusual. A response rate of four in five in a population defined by failure of everything else, with universal residual disease negativity among responders, describes an efficacy signal of a different order from incremental chemotherapy improvements [1,5]. Persistence of the transduced cells was observed beyond one year in responding patients, and multi-log expansion occurred across a two-log dose range without a relationship between infusion dose and expansion [5].

The adult product produced a remission rate of 71 per cent among 55 infused patients in its registration trial (Figure 2) [6,7]. The lower figure reflects an older and differently selected population rather than an established difference in product efficacy, since the two were never compared [6,8].

Manufacture itself is part of the outcome. Patients must undergo successful leukapheresis and the product must be made, which takes weeks during which the leukaemia continues. Reported response rates describe infused patients, so the intention-to-treat figure is lower than the headline, and analyses framed that way give a more honest picture of what a patient can expect at referral [20].

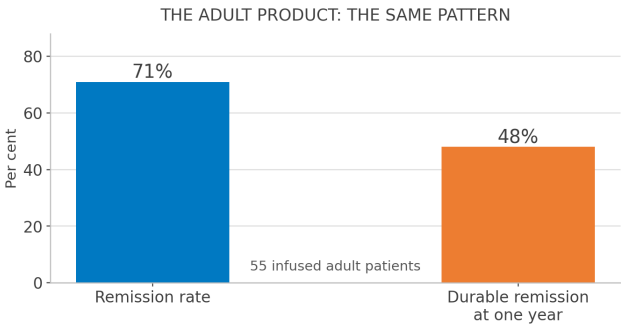


Figure 2: Remission and one-year durability with the adult product in 55 infused patients [6,7]

Durability is the limiting problem: Relapse-free survival at 18 months was 66 per cent (95% CI 52 to 77) and overall survival 70 per cent (95% CI 58 to 79) in the paediatric trial [11]. With longer follow-up the remission rate was reported as 82 per cent and three-year overall survival as 63 per cent (Figure 1) [12].

Setting an 81 per cent remission rate against 63 per cent survival at three years quantifies the gap. Nineteen patients relapsed before any additional anticancer therapy, and thirteen of those subsequently died [11]. Eight patients in remission proceeded to transplantation and eight received other therapy, so the survival figure reflects a mixture of strategies rather than CAR T cells alone [11].

The adult product showed the same pattern more starkly, with durable remission in 48 per cent at one year against a 71 per cent remission rate [7]. Roughly a third of initial responders had lost their remission within twelve months.

Long-term follow-up from a separate single-centre programme reported the same trajectory, with high initial remission followed by attrition, and established that durable remission without further therapy is achievable in a subset [22]. Identifying that subset in advance remains unresolved, and the genetics of the underlying leukaemia contribute in ways not yet incorporated into selection [25].

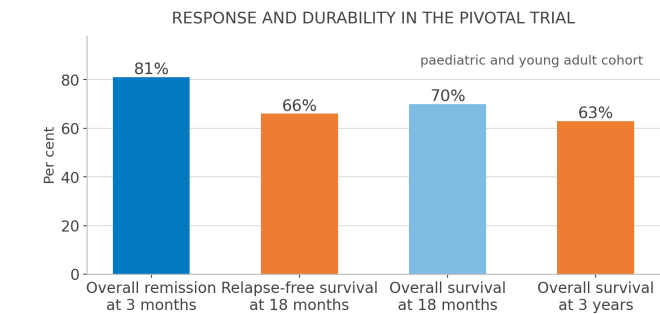


Figure 1: Remission and subsequent survival in the paediatric and young adult registration trial [5,11,12]

Study	n	Population	Principal reported finding
Maude et al. 2014 [4]	30	Single centre	First demonstration of sustained remissions
Maude et al. 2018 [5]	75	Paediatric, 25 centres	81% remission, all residual disease negative
Grupp et al. 2019 [11]	97 enrolled	Extended follow-up	18-month relapse-free survival 66%
Laetsch et al. 2023 [12]	—	Three-year follow-up	Remission 82%; overall survival 63%
Shah et al. 2021 [6]	55	Adult	71% remission; grade 3-4 CRS 24%, ICANS 25%
Roddie et al. 2024 [8]	Adult	Newer product	Alternative option with distinct design

Table 1: Principal studies reviewed, with population and the finding as reported by the original investigators

Toxicity is severe, frequent and largely reversible: Cytokine release syndrome occurred in 77 per cent of patients in the paediatric trial, with 48 per cent grade 3 or 4 by the Penn grading scale, and all episodes were reversible [11]. Grade 3 or 4 non-haematological events affecting more than 15 per cent of patients included neutropenia with fever above 38.3 degrees in 62 per cent within eight weeks of infusion, hypoxia in 20 per cent and hypotension in 20 per cent [11].

Neurological events were mostly transient, did not include cerebral oedema, and were more frequent in patients with

higher-grade cytokine release syndrome [5]. Grade 3 neurological events occurred in 13 per cent [11]. In the adult trial, grade 3 to 4 cytokine release syndrome and neurotoxicity were reported at 24 and 25 per cent respectively (Figure 3) [6,7].

Across the wider safety experience in this indication, the commonest adverse reactions were cytokine release syndrome in 79 per cent, hypogammaglobulinaemia in 43, infection in 41, pyrexia in 40, encephalopathy in 34 and hypotension in 31 per cent [13]. Hypogammaglobulinaemia reflects the on-target elimination of normal CD19 positive B cells and persists as long as the transduced cells do [5,13].

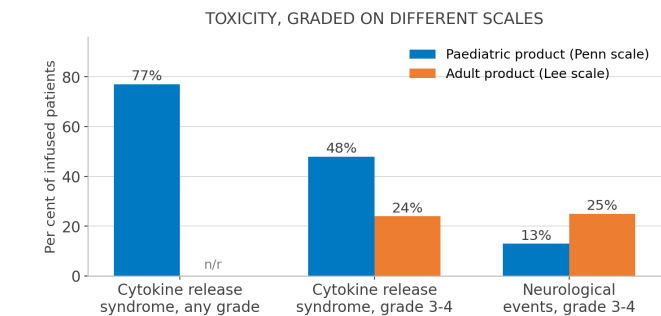


Figure 3: Reported toxicity for the two licensed products, graded on different scales [6,7,11]

When patients die: Twenty-five post-infusion deaths occurred in the paediatric trial, of which 2 fell within 30 days of infusion and 23 beyond it (Figure 4) [11]. In the wider safety dataset, of eleven reported deaths, seven were disease-related, three were attributed to infection and one to intracerebral haemorrhage [13].

That distribution matters for how the therapy is understood. The dramatic toxicities, cytokine release syndrome and neurological events, occur in the first weeks and are largely survivable [5,11]. The deaths mostly occur later and are mostly from relapsed leukaemia. A therapy discussed primarily in terms of its acute toxicity is failing patients principally through loss of disease control.

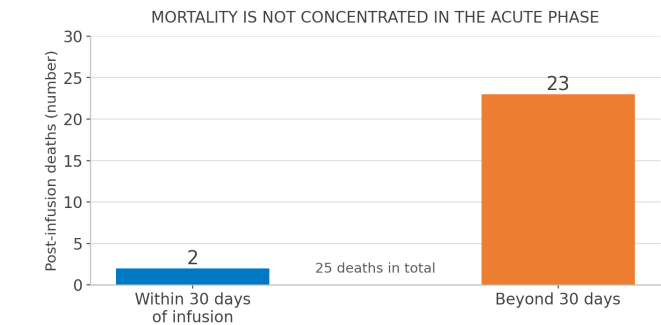


Figure 4: Timing of post-infusion deaths relative to the acute toxicity window [11]

Toxicity	Paediatric product	Adult product
Cytokine release syndrome, any grade	77%	Not reported comparably [6,11]
Cytokine release syndrome, grade 3-4	48% (Penn scale)	24% (Lee scale) [6,11]
Neurological events, grade 3 or above	13%	25% [6,11]
Febrile neutropenia, grade 3-4	62%	Not reported comparably [11]
Deaths within 30 days	2 of 25	Not reported comparably [11]

Table 2: Reported toxicity by product, with the grading scale used for each

Why remissions are lost: Relapse after CD19-directed therapy takes two forms and the distinction matters. Some patients relapse with disease that still expresses CD19, implying loss of the transduced cells or their function. Others relapse with CD19-negative disease, where acquired mutations and alternative splicing of CD19 remove the target while the leukaemia persists [18,19].

Antigen loss is the more troubling mechanism because it is not addressed by improving persistence. Genetic mechanisms of target antigen loss have been characterised directly in patients relapsing after therapy [19], and convergent acquired mutations with alternative splicing were shown to confer resistance while preserving the malignant clone [18]. A second infusion of the same product cannot help those patients.

Persistence of the transduced cells relates to product design. Formulation and dose have been examined in an intention-to-treat framework [20], and single-centre series using different constructs report differing persistence and toxicity [21,22]. High disease burden before infusion worsens outcome [23], which is one reason bridging strategy has become a focus.

What follows remission: Whether to consolidate a CAR T-cell remission with allogeneic transplantation is the most consequential unresolved question. Analysis of patients transplanted after CD19-directed remission reported a leukaemia-free survival advantage [17], and in the registration trial eight patients in remission proceeded to transplant while others did not [11], so the reported survival mixes both strategies.

Management of the acute toxicities is now well codified [10,24], with tocilizumab and corticosteroids used according to grade, and consensus criteria providing a common language that the registration trials lacked [14]. That standardisation should make the next generation of comparisons more interpretable than the current one.

Mechanism of failure	What it implies	Evidence
Loss of CAR T-cell persistence	Relapse with CD19-positive disease	Product design and dose studies [20,21]
CD19 antigen loss	Reinfusion of same product cannot help	Splicing and mutation analyses [18,19]
High disease burden at infusion	Worse survival despite response	Paediatric cohort analysis [23]
No consolidation after remission	Possible loss of durable benefit	Transplant comparison [17]

Table 3: Mechanisms by which remissions are lost and what each implies for management

Discussion

Two conclusions follow, and they point in different directions. The efficacy result is genuinely transformative: 81 per cent remission with universal residual disease negativity in patients who had failed everything available [5]. Nothing in conventional salvage approaches that.

The durability result is sobering. Three-year overall survival of 63 per cent against an 82 per cent remission rate means roughly a fifth of patients who achieved a deep remission subsequently lost it and died [12]. In adults the attrition is faster still, with 48 per cent durable at one year against 71 per cent responding [7]. The clinical problem has moved rather than been solved.

Why the products cannot be compared

Grade 3 or 4 cytokine release syndrome was 48 per cent for the paediatric product and 24 per cent for the adult one, which looks like a twofold difference [6,11]. The paediatric figure used the Penn scale and the adult figure the Lee scale, and these assign severity differently, so the comparison is uninterpretable as stated [9,14].

Consensus grading for cytokine release syndrome and neurotoxicity was published subsequently and is now standard [14], but the registration trials predate it. Any comparison of the two products on toxicity therefore requires regrading the source data, which has not been done. The populations also differ in age and in line of therapy, so even correctly graded figures would not settle the question [5,6].

Study limitations

The limitations belong to the underlying literature. Both registration trials were single-arm, so efficacy is compared against historical expectation rather than a concurrent control [5,6]. Patients require successful leukapheresis and manufacture, and those in whom the product fails or who deteriorate while waiting are not represented in the infused cohort, which inflates apparent efficacy [5,15]. Toxicity grading scales differ between the two products, and consensus

criteria postdate both trials [9,14]. Some patients proceeded to transplantation after remission, so survival cannot be attributed to the cell product alone [11]. And follow-up remains short relative to the survivorship of a mainly paediatric population, so late effects are incompletely described [12,16].

Two gaps deserve naming. No randomised comparison exists between the licensed products, nor between CAR T-cell therapy and allogeneic transplantation in patients eligible for both [5,6]. And no study reviewed here establishes whether consolidative transplantation after CAR T-cell remission improves durability, which is the question the relapse data raise most directly [11,17].

Conclusion

CD19-directed CAR T-cell therapy induces remission in 81 per cent of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia, with every responder residual disease negative, and in 71 per cent of adults. Durability is the limiting factor: relapse-free survival is 66 per cent at 18 months, overall survival 63 per cent at three years, and 48 per cent of adults remain in remission at one year. Cytokine release syndrome affects three quarters of patients and neurological events a substantial minority, but these are largely reversible and only 2 of 25 deaths occurred within 30 days of infusion. The therapy is failing patients through loss of disease control rather than through its acute toxicity, and the two licensed products were graded on different scales, so their published toxicity figures should not be compared.

Three questions define the next phase. Whether consolidative transplantation after remission improves durability, which one analysis suggests and no trial has tested [17]. Whether antigen loss can be pre-empted by targeting more than CD19, since a second infusion of the same product cannot help a patient whose leukaemia no longer expresses the target [18,19]. And whether reducing disease burden before infusion improves outcome, given that high burden predicts worse survival despite response [23].

None of these is a question about whether the modality works. It plainly does, in a population where nothing else did. They are questions about what should happen in the year after it works, which is where the remaining mortality now sits [11,12].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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