Received: 5 December 2023 | Accepted: 21 February 2024

DOI: 10.1111/bjh.19381

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

GUIDELINE

Practice guideline: Preparation for CAR T-cell therapy in children and young adults with B-acute lymphoblastic leukaemia

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Summary
The objective of this guideline, prepared by the ALL subgroup of the Advanced Cell Therapy Sub-Committee of BSBMTCT (British Society of Blood and Marrow Transplantation), is to provide healthcare professionals with practical guidance on the preparation of children and young adults with B-acute lymphoblastic leukaemia from the point of referral to that of admission for CAR T-cell treatment. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate the levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

KEYWORDS
B-acute lymphoblastic leukaemia, bridging chemotherapy, CAR T-cell

SUMMARY OF RECOMMENDATIONS

- Each patient deemed eligible for tisagenlecleucel treatment and funding based on the National Cancer Drug Funding should be discussed in the national CAR T-cell panel and subsequently referred to the most appropriate CAR T-cell centre based on capacity, distance and patient preference. 1C *(based on NHSE guidance)*
- Referral of the patient for the CAR T-cell therapy should include detailed information. It is recommended to use a standard pro forma specifically adapted for this purpose (Appendix S1). 1C *(Operational recommendation and not based on evidence)*
- Consideration should be made to make available a sample for confirmatory flow cytometry as well as share primers for IgH/TCR gene rearrangements and/or diagnostic/relapse material (or extracted nucleic acids) with the receiving CAR T-cell centre/their associated measurable residual disease (MRD) laboratory to facilitate MRD analysis post-infusion. *1C (Operational recommendation and not based on evidence)*
- Once the referral is received, prompt consultation at the CAR T-cell centre is recommended wherever possible and should be guided by factors including disease trajectory, lymphocyte recovery, etc. This consultation is to review the clinical background, current performance status, counsel parents about CAR T-cell therapy and consent for the leucapheresis and cell manufacture and storage. 1C
- All the prior treatment should be recorded, and minimum suggested intervals noted before leucapheresis. 1C *(Operational recommendation and not based on evidence)*

- We recommend use of 2 weeks of a three- (dexamethasone, vincristine, asparaginase) or four- (dexamethasone, vincristine, daunorubicin, asparaginase) drug induction in cases where reinduction therapy is required prior to harvest. Where reinduction therapy has already been received within the preceding 6 weeks, an alternative regimen from available bridging regimens should be considered. 1C (CLCN 2019 UK Relapse guidelines)
- Prior to leucapheresis, a lymphocyte count of $\geq 0.5 \times 10^9$/L and a CD3 count of $\geq 0.35 \times 10^9$/L are preferred, but a lymphocyte count of $\geq 0.3 \times 10^9$/L and a CD3 count of $\geq 0.15 \times 10^9$/L are acceptable. A 2–2.5 volume harvest is recommended. (1C)
- Bridging chemotherapy should be individualised and decided on a case-by-case basis considering response and toxicity to previous chemotherapy as well as the current level and rapidity of disease progression. 1C

In general, if the bone marrow disease burden is 5% or less, then oral 6-mercaptopurine and oral methotrexate as per UKALL2019 maintenance therapy with vincristine and dexamethasone pulses can be considered.[1] 1C/1D.

If the bone marrow disease is more than 5%, then Capizzi protocol with escalating methotrexate + vincristine and without asparaginase can be considered.[1] 1C/1D

- Infection during bridging should be treated aggressively, antifungal therapy should be given early consideration in patients with prolonged neutropenia, or prolonged steroid exposure (e.g. reinduction therapy) and appropriate prophylactic anti-microbial therapy, including anti-fungal prophylaxis, anti-PJP and antivirals should be instituted as per local policies for relapsed B-ALL. 1C
- In case of an out-of-specification product being notified for a patient, consultation with the NHSE OOS panel is required for all NHS patients and discussion in the national CAR T-cell panel is recommended. 1C *(Operational recommendation and not based on evidence)*

PATIENT IDENTIFICATION AND PREPARATION

Patient identification

Patients are generally identified through the national leukaemia or national paediatric ALL CAR T-cell therapy panel which convene on an alternate 2 weekly basis. Patients may also be identified through local MDT networks.

Urgent cases may be circulated by email to the CAR T-cell panel members for consideration between fortnightly meetings. However, to maintain transparency about eligibility and complete data capture of all patients considered for this therapy, all patients not initially identified in the CAR T-cell therapy MDT should be discussed in the next planned meeting.

Assessment of patient eligibility

Eligibility criteria are available via NHS England national drug funding list (Table 1).[2]

The Blueteq high-cost drug (HCD) management system is in use for Tisagenlecleucel. It is the responsibility of the CAR T-cell centre to complete the relevant online forms during a patient's pathway. The initial form (TIS01a_v1.2) should be submitted upon approval by the CAR T-cell panel that the patient is eligible and proceeding to leucapheresis and manufacture. The second part of the form (TIS01b_v1.1) should be completed on admission to register the infusion so that the treating centre is reimbursed for the cost.

Recommendation

- Each patient deemed eligible for tisagenlecleucel treatment and funding based on the National Cancer Drug should be discussed in the national CAR T-cell panel and subsequently referred to the most appropriate CAR T-cell centre based on capacity, distance and patient preference. 1C *(based on NHSE guidance)*

REFERRAL TO CAR T-CELL CENTRE

The selection of CAR T-cell centre is made on geographic grounds, centre capacity and patient preference. At present, there are only four centres across UK providing CAR T-cell therapy in patients less than 16 years of age, they might need to travel >1 h from their home. It would be useful to inform the patient/family at this point of any hospital accommodation that might be available to them to access, and any support that is available from charities, for example, CAR-T Away from Home Service—Leukaemia Care (Appendix S2).

Information required at referral

Please see CAR T-cell therapy pro forma in Appendix S1, which standardises the approach to information gathering. Relevant information relates to that required to expedite leucapheresis and associated procedures. Response to prior therapy and toxicities should be determined along with information on concomitant drugs which may pose interactions for bridging or anti-microbial prophylaxis or timings relevant for washout prior to leucapheresis (Figure 1). Information used to confirm eligibility for CAR T-cell therapy should be provided as well as assessing adequate organ function, performance status and matters which are of relevance to the holistic care of the patient and their family. Upon referral, the need for anaesthesia/sedation for the leucapheresis, both for an additional line (vascath) placement and for the collection procedure in younger children should be discussed with the referring physician and the parents.

TABLE 1 Eligibility criteria for patients aged 25 years and under with B lineage acute lymphoblastic leukaemia (adapted from National Cancer Drugs Funding list).[2]

Tisagenlecleucel	**Criteria for use**		
	Philadelphia positive or negative B lineage acute lymphoblastic leukaemia	Second or more bone marrow relapse following conventional doses of front-line therapy (chemotherapy or monoclonal antibody therapy) **OR** Bone marrow relapse after allogeneic stem cell transplantation (SCT) with a period of 4 months having passed since the time of transplant and planned time of CAR T-cell infusion Primary refractory disease, not achieving complete remission after 2 cycles of standard chemotherapy for newly diagnosed B-ALL **OR** Secondary refractory disease, not achieving a complete remission after at least one cycle of standard relapsed chemotherapy Philadelphia-positive B-ALL that is refractory to 2 lines of primary chemotherapy with tyrosine kinase inhibitor (TKI) or refractory to re-induction chemotherapy with TKI **OR** Relapsed post-SCT despite treatment with standard therapy plus tyrosine kinase inhibitors (TKI) Relapsed disease and ineligible for allogeneic SCT due to comorbid disease, but still fit enough for CAR T-cell therapy **OR** Contraindication to allogeneic SCT conditioning or lack of suitable donor	CD19-positive disease in the bone marrow detectable by flow cytometry (not isolated extramedullary ALL relapse and with no active CNS involvement)

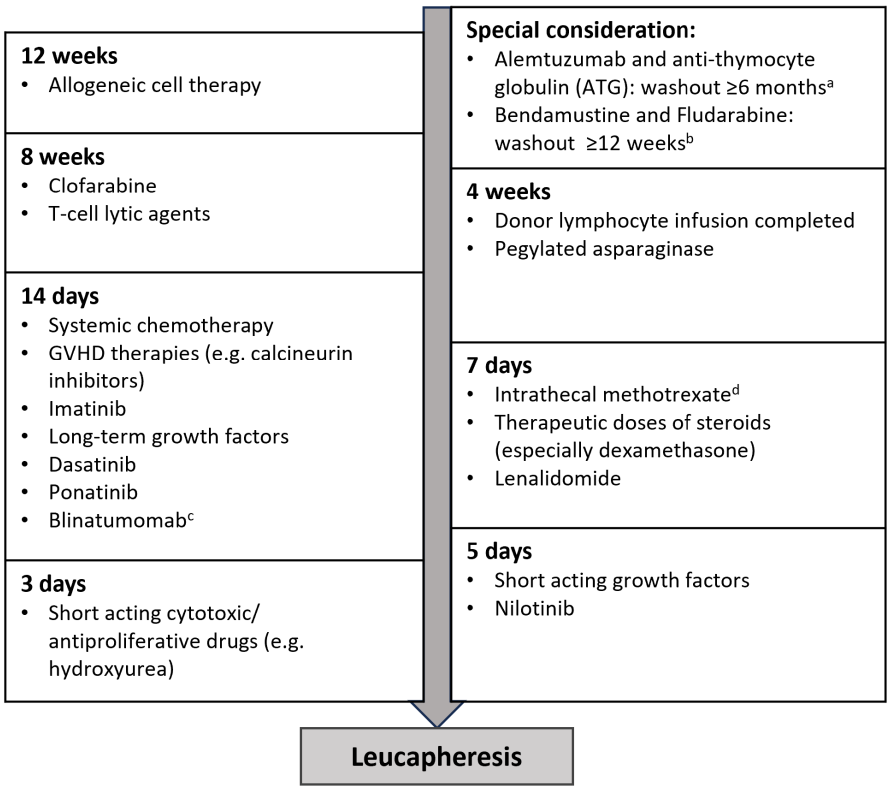

FIGURE 1 Recommended intervals from therapy to leucapheresis.[6,7] [a]Alemtuzumab and ATG (T-cell lytic agents): Allow adequate washout and avoid use for ≥6 months prior to leucapheresis and consider the potential prolonged effects on T cells. [b]For bendamustine and fludarabine, allow adequate washout and avoid use for ≥12 weeks prior to leucapheresis due to the potential long-term effects on T cells; however, there are limited data in the context of CAR-T-cell therapy for these agents. [c]Although blinatumomab half-life is short (~2 h), it is recommended to washout 1–2 weeks prior to leucapheresis. [d]If indicated, intrathecal cytarabine can be given up to a day prior to leucapheresis. For an intravenous cytarabine dose <100 mg/m^2, a washout of 7 days is recommended; for a dose ≥100 mg/m^2, a washout of 14 days is recommended.

If the patient is undergoing disease restaging it is worth considering if a sample should be assessed for confirmatory flow cytometry at the laboratory most used to supporting the allocated CAR T-cell centre. Detailed interpretation of the leukaemia-associated immunophenotype (LAIP) may be required, especially to exclude CD19-negative populations, assess for intensity of CD19 expression as well as to provide samples for MRD analysis by IgH/TCR gene rearrangement PCR since both flow and molecular MRD tests contribute disease monitoring post CAR T-cell infusion, as well as planning for bridging chemotherapy. It is our practice to request samples prior to harvesting/starting bridging therapy as a result. In the case of quantitative PCR for IgH/TCR gene rearrangements, there would need to be a transfer of primers and diagnostic/relapse material, or nucleic acids isolated at these times to facilitate quantitative analysis. In case disease samples could not be provided, flow cytometry files upon last disease detection should be shared for assessment of CD19 expression and to facilitate LAIP assessment post infusion.

First consultation: Detailed clinical background and current clinical status check

Once eligibility is confirmed, the patient should be reviewed at the CAR T-cell centre as soon as possible[3] considering *factors like disease trajectory, lymphocyte recovery, etc*., with a view to harvesting before the need for reinduction chemotherapy. Unless there is a high circulating blast count (>10–20 × 10^9/L), it may be preferable to proceed to harvest directly. In this guideline, we have assumed that active CNS disease[4] will have been treated prior to review since there is a minimum washout of 7 days required after intrathecal therapy before leucapheresis (Figure 1), and therefore, leucapheresis is best scheduled once CNS1 or CNS2 status has been achieved and intervals between CNS-directed therapy are in any case being increased. At a first consultation, it is important to verify the clinical background (Table 2) and current clinical status (Table 3) of the patient.

The interval from last chemotherapy or immunosuppressive drugs should be documented and consideration given to the recommended minimum intervals required from various therapies to leucapheresis (Figure 1). N.B. These are for guidance only and may change in accordance with manufacturer guidance. If for any reason the minimum interval cannot be respected, it is suggested to inform a medical representative at the manufacturing company and liaise with the National Paediatric ALL CAR T-cell panel for advice.

In terms of complications, it is important to ascertain if any history of prior probable or proven fungal infection, resistant Gram-negative organisms or any other atypical infections, any predisposition to mucositis or neurological complications which may warrant neuroimaging as a baseline.

TABLE 2 Details of clinical background.

• History of presentation with B-ALL, CNS status, complications at presentation, prognostic risk classifications (NCI, cytogenetic and early MRD response)
• Nature of consolidation/intensification therapy, complications, response
• History of first relapse, interval to and site of relapse (CNS status) leading to relapse disease risk classification
• Evidence of cytogenetic evolution and/or confirmation that relapse is not a second or donor-derived leukaemia from IgH gene rearrangements, chimerism analysis
• Nature of re-induction, consolidation and re-intensification therapy, complications, response at end of induction, consolidation
• Date of transplant, conditioning regimen, donor, degree of HLA match, cell dose, MRD status immediately prior to transplant, immunosuppressive agents used and dates of withdrawal, nature of complications including details of GVHD (if applicable)
• Date of second relapse, interval to and site of relapse (CNS status) leading to disease risk classification, therapy given (if any) with dates for this
• Details of subsequent relapses
• Relevant toxicities, cumulative doses for anthracycline (in relation to subsequent cardiac toxicity) and alkylating agents (in relation to fertility considerations)
• Previous therapy with Blinatumomab requires specific mention. In case of previous treatment, phase of treatment, number of courses administered, response after each course, need to switch to another treatment due to non-response and complications[5]
• Past medical history. Careful consideration should be given to evidence of cancer predisposition syndromes and relevant testing
• Anaesthetic history
• Developmental, family and social history
• Language barriers

TABLE 3 Current clinical status.

1. Performance status
2. Organ (cardiac/hepatic/renal) dysfunction
3. Current neurological status
4. Peripheral blood counts including B- and T-cell subset analysis
5. Virological status, considering viral testing relevant to autologous cellular therapy
6. Central venous access and line placement history
7. Current medications (to assess interactions with bridging, antimicrobial prophylaxis)

HSCT donor search

Patients who have not received prior HSCT should have an up-to-date search conducted at their allocated transplant centre in case of poor persistence or relapse post CAR-T-cell therapy and need for rapid consideration of HSCT. Patient tissue typing, donor status (with confirmatory samples), date of most recent search and HLA-specific antibody test results should be shared with the CAR T-cell centre as part of referral in case further liaison is required with the HSCT

centre during patient follow-up. These details are included in the referral pro forma (Appendix S1).

Assessment of blood groups post-HSCT

Institutional guidelines should be followed to ensure the current grouping is adhered to when requesting blood products for patients post-HSCT. Relevant donor information, including patients pretransplant blood group and donor blood group should be provided upon referral to the CAR T-cell centre.

Consent

At the first consultation, we recommend to discuss the whole process associated with CAR T-cell therapy (leucapheresis, bridging chemotherapy, lymphodepletion and CAR T-cell infusion) with associated toxicities expected as well as outcomes of this intervention as compared to other potential therapies such as second transplant or symptom care. This is because to take consent for leucapheresis, the patient and their family need to have a clear understanding of the entire process. It also gives an opportunity to cover the information required in advance of taking consent for CAR T-cell therapy, which may then obtained at a second appointment.

Where possible, an information leaflet should be provided to the parents in advance of the initial consultation to reinforce the information given and provide an opportunity for discussion. Consent for virological/syphilis screening, for leucapheresis (see Table 4) as well as company-specific consent for transfer of the leucapheresis product and any associated data required for maintaining the chain of identity are required at this point. This provides the advantage of facilitating launch of the CAR T-cell manufacturing request with the company thus securing the leucapheresis collection date and manufacturing slots. Leucapheresis consent should also cover the low but absolute rate of failure to generate a product or of generating one which does not meet all the release requirements for a licensed product. In this eventuality, an application can be made to infuse this off licence, following MHRA/NHSE and local approvals as necessary.

At the initial meeting, an assessment of venous access should be made. Depending on the age of the patient, this should either be undertaken by the IR team or the apheresis team with considerations given to the number of sites of prior central lines and prior complications. Patients should be counselled about potential need for central venous access either in advance or on day of procedure to allow collection to take place. At the first assessment, patients and families should be introduced to their specialist nurse where possible and given contact details for the CAR-T Team.

Re-induction therapy (if required)

Where re-induction therapy is required prior to harvest, either because of a delay to harvest or significant symptoms, then we would recommend 2 weeks of a three- or four-drug induction as per bridging guidelines below. Disease reassessment should be undertaken after 2 weeks, and in the context of adequate disease response, a therapy holiday started at this point to facilitate a harvest as soon as the maximum intervals from chemotherapy allow (Figure 1). The patient should be commenced on prophylactic anti-fungal therapy as well as prophylactic anti-PJP and anti-viral therapy as per institutional guidance.

Recommendations

- Referral of the patient for the CAR T-cell therapy should include detailed information. It is recommended to use a standard pro forma specifically adapted for this purpose (Appendix S1). *1C (Operational recommendation and not based on evidence)*
- Consideration should be made to make available a sample for confirmatory flow cytometry as well as share primers for IgH/TCR gene rearrangements and/or diagnostic/relapse material (or extracted nucleic acids) with the receiving CAR T-cell centre/their associated measurable

TABLE 4 Considerations for leucapheresis consent.

Infectious screening for cell therapy laboratory	Consent for infectious screening, as per HTA requirements and local laboratory policy.
Need for additional central venous access ('Vascath')	Discomfort Infection Bleeding/bruising at site of line Damage to local structures Failure to insert
ACD-A as an anti-coagulant in apheresis circuit	Alterations in blood calcium/other salt disturbance, the need for replacement Alterations in blood pressure Bleeding or bruising
Apheresis process	Need for transfusion support (blood or platelets)
Other	Need for anaesthesia/sedation for the leucapheresis, both for an additional line(vascath) placement or for the collection procedure in younger children Failure to harvest adequate cells/need for additional harvest days

residual disease (MRD) laboratory to facilitate MRD analysis post-infusion. *1C (Operational recommendation and not based on evidence)*
- Once the referral is received, prompt consultation at the CAR T-cell centre is recommended wherever possible and should be guided by factors including disease trajectory, lymphocyte recovery, etc. This consultation is to review the clinical background, current performance status, counsel parents about CAR T-cell therapy and consent for the leucapheresis and cell manufacture and storage. 1C
- All the prior treatment should be recorded, and minimum suggested intervals noted before leucapheresis. 1C *(Operational recommendation and not based on evidence)*
- We recommend use of 2 weeks of a three- (dexamethasone, vincristine, asparaginase) or four- (dexamethasone, vincristine, daunorubicin, asparaginase) drug induction in cases where re-induction therapy is required prior to harvest. Where re-induction therapy has already been received within the preceding 6 weeks, an alternative regimen from available bridging regimens should be considered. 1C (CLCN 2019 UK Relapse guidelines)

LEUCAPHERESIS PROCEDURE

It is out with the scope of these guidelines to consider the details of the leucapheresis itself, and resources are available from Novartis/ NHSBT/Advanced Therapy Treatment Centres (ATTC) where necessary. The manufacturing company should be informed where patients <10 kg are harvested, and consideration should be given to ordering packed red blood cells to facilitate priming the apheresis machine prior to the harvest. Irradiated blood products should be used from at least 7 days prior to until leucapheresis is completed.

In general, we recommend a lymphocyte count of $\geq 0.5 \times 10^9$/L, and a CD3 count of $\geq 0.35 \times 10^9$/L prior to a 2–2.5 volume harvest.[7]

If lower, for example, CD3 count of 0.15×10^9/L, the harvest may well still be successful,[8,9] but the volume of processing may be increased to improve yields, and planning for additional days of harvest are recommended.[10] There are other variables which can be adapted to improve the yield of the harvest, for example, haematocrit.[7,11] We suggest working closely with the local apheresis team, providing feedback on the yield and proportion of T cells to optimise collection protocols as much as possible to maximise yield and minimise contaminating cell populations which can have a negative impact on the success of manufacture.[12]

Recommendations

- Prior to leucapheresis, a lymphocyte count of $\geq 0.5 \times 10^9$/L and a CD3 count of $\geq 0.35 \times 10^9$/L are preferred, but a lymphocyte count of $\geq 0.3 \times 10^9$/L, and a CD3 count of $\geq 0.15 \times 10^9$/L are acceptable. A 2–2.5 volume harvest is recommended. (1C)

BRIDGING CHEMOTHERAPY AND WORK UP INVESTIGATIONS

Selection of the best bridging therapy for an individual patient will depend on past medical history of toxicities/allergies and intolerances as well as consideration of the pace of disease progression.[13] To benefit from relevant UK experience, where possible bridging therapy options should be discussed with the national CAR T-cell panel. Careful disease monitoring is required to demonstrate response in the face of bulk disease and baseline measurements prior to CAR T-cell infusion. The aims of bridging chemotherapy for CAR T-cell therapy are different to those employed in other front-line or relapse management:

- To effectively reduce disease burden (though deep remission is not required)
- To avoid persisting/profound neutropenia (may result in infectious complications)
- To avoid significant toxicity in terms of mucositis, cardiac/renal/hepatic impairment
- To maintain quality of life, with out-patient management for most of the bridging period if possible
- To avoid profound B lymphopenia at the point of CAR T-cell infusion (in which case CAR T-cell expansion may be limited)

There is clear evidence from retrospective data that those who achieve a tumour burden of <5% have better outcomes after CAR T-cell therapy.[14] However, there is no evidence that successive cycles of bridging therapy to achieve this provide any benefit.[15] This may reflect the aggressive nature of more refractory disease. In contrast, there is evidence that additional bridging cycles may contribute to additional toxicity[15] which can delay timely progression to CAR T-cell infusion.

Suggested bridging chemotherapy protocols

For lower levels of disease (5% BM blasts or less)

- Oral 6-mercaptopurine and oral methotrexate as per ALL maintenance therapy ± vincristine and dexamethasone pulses
- TKI + oral maintenance with 6-mercaptopurine/oral methotrexate for Philadelphia + ALL

N.B. Selection of TKI should consider the presence of BCR-ABL mutations (incidence of up to 80% in relapsed Ph + ALL)[16] as well as site of relapse.

For patients with higher levels of disease (more than 5%)

Consider discussing bridging strategies for patients with significant prior toxicity or refractoriness in the National Paediatric ALL CAR T-cell panel meeting. Hybrid regimes may be needed to effectively bridge the interval until lymphodepletion.

- Three to four-drug reinduction therapy for 2–4 weeks, four drugs for those ≥10 years of age or WCC ≥50 x 10^6/L. Suggest disease response assessment at 2 weeks into therapy to limit further doses of asparaginase/anthracycline if disease response kinetics are favourable.
- Capizzi protocol escalating methotrexate (starting at 100 mg/m^2 IV, dose escalated by 50 mg/m^2 every 10 days for a total of 5 doses)[17] + vincristine (without asparaginase to avoid hypersensitivity/toxicity)
- Single doses of inotuzumab (if CD22+ disease), aiming for disease bulk reduction. The dose and intervals between inotuzumab doses should be titrated carefully as weekly cycles over 3 weeks can cause profound B-cell aplasia and which may in turn contribute to suboptimal CAR T-cell expansion.
- Intermediate- to high-dose cytarabine, for example, 6–18 g/m^2 total dose as 3 g/m^2 infusions given every 12 hours. This may need to be repeated after 3–4 weeks depending on blast and count recovery.
- Etoposide/cyclophosphamide as per week 7 ALLR3 consolidation,[18] that is, Cyclophosphamide, d1–5440 mg/m^2 iv + Etoposide, d1–5100 mg/m^2 iv.

N.B. The management guidelines for bridging protocols may need to be adapted from their use in front-line therapy. In front line therapy, patients may have greater bone marrow reserve than a patient in frank relapse being bridged to CAR T-cell therapy. We therefore waive threshold FBC parameters needed before proceeding with chemotherapy doses but maintain those relevant for organ dysfunction or mucositis.

Fertility preservation techniques

Once bridging therapy has been selected, consideration of the doses of chemotherapy needed at lymphodepletion as well as in prior therapy allows a basis for considering if fertility preservation techniques, such as ovarian and testicular cryopreservation, sperm banking, are recommended in accordance with institutional policies.[19]

Disease reassessment and intrathecal therapy during bridging

We recommend assessing a bone marrow and giving intrathecal therapy at 2 weeks into the bridging period to assess disease response. If there are any delays to CAR T-cell infusion, we recommend intrathecal therapy every 4 weeks unless recent CNS relapse, when more frequent intrathecal therapy may be needed. In any patient with a history of leucoencephalopathy or intensive prior CNS-directed therapy, consideration should be given to reducing exposure to methotrexate wherever possible, for example, by converting to prophylaxis with hydrocortisone and cytarabine or alternating regimens, but this should be weighed against adequate disease control.

Complications during bridging chemotherapy

In case of febrile neutropenia, there should be a high suspicion of atypical infection, for example, fungal infection, even in the absence of suggestive signs. We suggest empiric therapy is started at an earlier time point than might be considered for front-line therapy. This is in view of the heavy treatment burden these patients have generally faced by the time of bridging, for many including stem cell transplant (SCT).[15] In the case of persisting fevers, we would suggest early involvement of microbiology and infectious diseases teams, along with a careful history including travel history to help identify relevant investigations for an extended infectious screen to include CMV, EBV and adenoviral PCRs in blood and imaging studies.

As discussed above, as a minimum bridging phase prophylaxis should include prophylactic anti-fungal therapy as well as prophylactic co-trimoxazole and anti-virals as per institutional policy.

Planning for CAR T-cell therapy admission

Timing

We assume there will be a 4- to 5-week interval between collection of the cryopreserved product and admission for lymphodepletion.[13] When organising for this admission, it is important to consider:

- Dates of last predicted therapy and minimum intervals from drugs to infusion (from ELIANA trial, as reported in Table 5).[20]
- Allowing B-cell recovery, if possible, prior to admission for CAR T-cell therapy. This is not necessary or warranted where there remains a burden of detectable disease or rapid disease progression.[21]
- We recommend not starting lymphodepletion until the product has been successfully received and QC checked by the pharmacy or the cell therapy team, in case of packaging damage or other concern.

Reviews and CAR T-Cell therapy consent

During the bridging period, the patient and their family should be reviewed at least once by the CAR T-cell

TABLE 5 Minimum suggested intervals between systemic therapies and CAR T-cell infusion (taken from ELIANA protocol).[20]

Time interval prior to infusion	Medication
>72 h prior to infusion	Therapeutic systemic doses of steroids, TKIs, hydroxycarbamide
>1 week	Vincristine, 6-mercaptopurine, 6-thioguanine, Methotrexate <25 mg/m^2, Cytosine arabinoside <100 mg/m^2/day, Asparaginase (non-pegylated), CNS prophylactic therapy
>2 weeks	Clofarabine, cytosine arabinoside >100 mg/m^2, Anthracyclines, cyclophosphamide, methotrexate ≥25 mg/m^2, non-CNS related radiotherapy
>4 weeks	Systemic GVHD therapies, pegylated asparaginase
>6 weeks	Donor leucocyte infusions
>8 weeks	CNS-directed radiotherapy, anti T-cell antibodies (e.g. alemtuzumab)

centre, to make a baseline clinical assessment and so consent for CAR T-cell therapy can be obtained/confirmed after a further discussion. Where the patient is geographically distant from the CAR T-cell centre, this may not be feasible, in which case, consent may be obtained at leucapheresis or on admission for CAR T-cell therapy. Consent for CAR T-cell therapy should include a discussion of:

- Admission length
- Lymphodepleting agents and their side effects (in particular, GI upset/cytopenias/infections/neurotoxicity/haemorrhagic cystitis/secondary malignancy/reduced fertility)
- CAR T-cell toxicities including CRS/ICANs/hypogammaglobulinemia/prolonged cytopenia
- Need for ICU admission to manage organ dysfunction in the context of these toxicities
- Prolonged cytopenia related to CAR T-cell therapy, which can be persistent or occur after 28 days and may require supportive management (growth factor support, blood product support, prophylactic antimicrobials)
- In TYA patients, discuss that they will not be able to drive for at least 1 month post-CAR-T-cell infusion due to risk of neurotoxicity.
- In TYA patients, discuss the need for contraception as per local policies.
- Failure to respond
- Likely event-free and overall survival at 12 and 24 months respectively
- Likelihood of need for adjunctive therapy in the case of short persistence of CAR T cells (as measured by early loss of B-cell aplasia within 6 months of infusion) or relapse
- Likelihood of salvage in the case of emergence of MRD or frank relapse, including with CD19-negative or lineage switch leukaemia
- Frequency of blood and bone marrow testing post CAR-T-cell infusion
- Unanticipated genotoxicity
- Secondary malignancy
- Replication competent lentivirus
- Testing positive for HIV PCR-based tests
- Alternative therapies or pathways available, including symptom care, SCT as appropriate

Allied health professional (AHP) assessment and planning

The complex medical history and long prior treatment course in many CAR T-cell patients means there is a strong need for a multidisciplinary approach to preparing the patient for CAR T-cell therapy. Patients may be referred to a joint AHP clinic during their bridging phase whereby they meet with the AHP's listed below and an admission plan is made. The plan includes involvement from members of the AHP team to promote physical, emotional and psychological well-being with the aim of promoting an inpatient environment that allows growth, development and maintaining activity.

AHP's involved:

- Physiotherapy
- Occupational therapy
- Speech and language therapy
- Social work
- Psychology
- Play specialist
- Dietician
- Hospital School

Several charities work with families undergoing therapy for advanced ALL. These include CCLG, leukaemia care, teenage cancer trust, young lives versus cancer which provide information on emotional, financial and peer to peer support (Appendix S2). Additionally, there are numerous parents and patient-centred videos which can be accessed.

Workup investigations

We recommend the following workup (Table 6):

Where possible, images should be reviewed by the CAR T-cell centre with involvement of specialist colleagues (i.e. neurology) who will be jointly reviewing the patient during the CAR-T admission.

TABLE 6 Investigational workup during bridging therapy.

MUGA/ECHO/GFR
CT chest/lung function as per local protocols ± USS abdomen
Formal GFR assessment, particularly for any patient with a prior history of significant AKI
Chimerism analysis on PB/BM (if applicable)
Hearing test
Baseline neurological/cognitive assessment
MRI brain with contrast in any child with neurological involvement or neurological signs/past medical history of neurological complications, and in all treated <2 years of age
MRI spine for those with past involvement
Transfusion record, especially for post-transplant patients

Other bridging phase considerations

We recommend meticulous documentation of any allergic reactions with blood products and if necessary, a trial of therapy without steroid cover during the bridging period in order that routine steroid cover following the infusion of CAR T cells can be completely avoided.

Recommendation

- Bridging chemotherapy should be individualised and decided on a case-by-case basis considering response and toxicity to previous chemotherapy as well as the current level and rapidity of disease progression. 1C

In general, if the bone marrow disease burden is 5% or less, then oral 6-mercaptopurine and oral methotrexate as per UKALL2019 maintenance therapy ± vincristine and dexamethasone pulses can be considered.[1] 1C/1D.

If the bone marrow disease is more than 5%, then Capizzi protocol with escalating methotrexate + vincristine and without asparaginase can be considered.[1] 1C/1D.

Infection during bridging should be treated aggressively, anti-fungal therapy should be given early consideration in patients with prolonged neutropenia, or prolonged steroid exposure (e.g. reinduction therapy) and appropriate prophylactic anti-microbial therapy, including anti-fungal prophylaxis, anti-PJP and anti-virals should be instituted as per local policies for relapsed B-ALL. 1C.

FAILURE OF MANUFACTURE/OUT OF SPECIFICATION (OOS) PRODUCT NOTIFICATION

The manufacturing failure rate for tisagenlecleucel is low with a 98% manufacturing success rate (MSR) in a 6-month period in 2022 and all products were ultimately shipped either as Kymriah or an OOS product to all patients (Novartis, unpublished communication).

During bridging, information may be received that the manufacture has failed or that the product has not met release criteria. In the case of manufacturing failure, it is worth consulting the National Paediatric ALL CAR T-cell panel to discuss likely causative factors before considering feasibility of recollection. In the case of an OOS product, there is an NHSE approval pathway to follow which involves consultation with the NHSE OOS panel. This panel considers the nature of the OOS criterion as well as the feasibility of recollection before making a recommendation to recollect or proceed to infusion recommended this or proceeding to infuse the OOS product.

Recommendation

- In case of an out-of-specification product being notified for a patient, consultation with the NHSE OOS panel is required for all NHS patients and discussion in the national CAR T-cell panel is recommended. 1C *(Operational recommendation and not based on evidence)*

AUTHOR CONTRIBUTIONS

Sara Ghorashian chaired the writing group. All authors contributed to writing, editing and reviewing the manuscript, including the final submission.

ACKNOWLEDGEMENTS

The authors wish to thank Juliana Silva and Deena Iskander for their invaluable feedback to the manuscript. All CAR T centres delivering tisagenlecleucel for this indication were consulted and are represented in the authorship.

FUNDING INFORMATION

There was no funding associated with this work.

CONFLICT OF INTEREST STATEMENT

A.K.M. is supported by MRC. M.O.R. received honoraria from Kite/Gilead, Novartis, Janssen; travel and conference expenses from Kite/Gilead and is on advisory board for Kite/Gilead, Autolus. E.N. received honoraria from Kite/Gilead, Novartis, BMS/Celgene/Sanofi/Takeda; research grant from Kite/Gilead and is on DSMB for Autolus. S.W. received honoraria from Janssen. D.M. consulted for Pfizer, Novartis and Kite/Gilead. P.J.A. received royalties on patent licensed by Autolus PLC. S.G. received speaker honoraria from Novartis and patents and royalties from UCLB. All other authors have no competing interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mishra AK, Burridge S, Espuelas MO, O'Reilly M, Cummins M, Nicholson E, et al. Practice guideline: Preparation for CAR T-cell therapy in children and young adults with B-acute lymphoblastic leukaemia. Br J Haematol. 2024;00:1–10. https://doi.org/10.1111/bjh.19381