GUIDELINE ARTICLE

Approaches for bridging therapy prior to chimeric antigen receptor T cells for relapsed/refractory acute lymphoblastic B-lineage leukemia in children and young adults

Tobias Feuchtinger,[1-3] Peter Bader,[4] Marion Subklewe,[2,5] Maike Breidenbach,[1,2] Semjon Willier,[1,3] Markus Metzler,[2,6] Nicola Gökbuget,[7] Julia Hauer,[2,8] Fabian Müller,[2,9] Paul-Gerhardt Schlegel,[2,10] Michael Frühwald,[2,11] Christoph Schmid,[2,12] Anja Troeger,[2,13] Claudia Baldus,[14] Roland Meisel,[15] Annette Künkele,[16] Max Topp,[2,17] Jean-Pierre Bourquin,[18] Gunnar Cario,[19] Arend von Stackelberg[16] and Christina Peters[20]

[1]Department of Pediatric Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Dr. von Hauner Children's Hospital, University Hospital, LMU Munich, Munich, Germany; [2]Bavarian Cancer Research Center (BZKF), R/R ALL Study Group, Germany; [3]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; [4]Goethe University, University Hospital, Department for Children and Adolescents, Division for Stern Cell Transplantation, Immunology and Intensive Care, Frankfurt, Germany; [5]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [6]Department of Pediatrics and Adolescent Medicine, University Hospital Erlangen, Erlangen, Germany; [7]Department of Medicine II, Hematology/Oncology, Goethe University, Frankfurt, Germany; [8]Department of Pediatrics and Children's Cancer Research Center, TUM School of Medicine, Children's Hospital Munich Schwabing, Technical University of Munich, Munich, Germany; [9]Department of Internal Medicine 5, Hematology and Oncology, University Hospital of Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg (FAU), Erlangen, Germany; [10]University Children's Hospital Wuerzburg, Wuerzburg, Germany; [11]Pediatrics and Adolescent Medicine, Swabian Children's Cancer Center, University Medical Center Augsburg, Augsburg, Germany; [12]Department of Internal Medicine, University Medical Center Augsburg, Augsburg, Germany; [13]Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Regensburg, Regensburg, Germany; [14]Department of Internal Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany; [15]Division of Pediatric Stern Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; [16]Charite-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Department of Pediatric Oncology and Hematology, Berlin, Germany; [17]Department of Medicine II, University Hospital of Würzburg, Würzburg, Germany; [18]Department of Oncology, University Children's Hospital Zürich, Zürich, Switzerland; [19]Department of Pediatrics, University Medical Center Schleswig-Holstein, Campus Kiel, Germany, Kiel, Schleswig-Holstein, Germany and [20]St. Anna Children's Hospital, St. Anna Children's Research Institute, Medical University Vienna, Vienna, Austria

Correspondence: T. Feuchtinger
tobias.feuchtinger@uniklinik-freiburg.de

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Abstract

The ongoing development of immunotherapies, including chimeric antigen receptor (CAR) T cells, has revolutionized cancer treatment. In pediatric relapsed/refractory B-lineage acute leukemia antiCD19-CAR induce impressive initial response rates, with event-free survival plateauing at 30-50% according to long-term follow-up data. During the interval between diagnosis of relapse or refractoriness and CAR T-cell infusion, patients require a bridging therapy. To date, this therapy has consisted of highly variable approaches based on local experience. Here, in an European collaborative effort of pediatric and

adult hematologists, we summarize current knowledge with the aim of establishing guidance for bridging therapy. We discuss treatment strategies for different subgroups of patients, the advantages and disadvantages of low- and high-intensity regimens, and the potential impact of bridging therapy on outcomes after CAR T-cell infusion. This guidance is a step towards cross-institutional harmonization of bridging therapy, including personalized approaches. This will allow better comparability of clinical data and increase the level of evidence for the treatment of children and young adults with relapsed/refractory B-lineage acute leukemia until they can receive CAR T-cell infusion.

Introduction

Treatment of children and young adults with relapsed/refractory (R/R) B-lineage acute lymphoblastic leukemia (B-ALL) remains a challenge.[1] Despite significant progress, relapse remains the leading cause of treatment failure while primary resistant ALL is relatively rare in children and young adults. The development of gene-engineered T cells with a chimeric antigen receptor (CAR) has revolutionized cancer immunotherapy.[2] In recent years, treatment regimens for patients with R/R B-ALL have improved significantly, particularly with the approval of antiCD19-CAR T-cell therapy by the Food and Drug Administration and the European Medicines Agency. Initial response rates to anti-CD19-CAR T-cell therapy are high.[3,4] However, the majority of patients relapse following CAR T-cell treatment, so the 5-year event-free survival is 30-50% in pediatric cohorts and approximately 20% in adult cohorts.[5-8]

It may take several weeks to manufacture CAR T cells before the start of lymphodepleting chemotherapy and the subsequent infusion of the CAR T cells. Anti-leukemic treatment during this period can be divided into a first phase until leukapheresis and a second phase ("bridging therapy") until the start of lymphodepleting therapy (Figure 1). Especially prior to leukapheresis, treatment should not reduce T-cell fitness. The optimal bridging therapy has not yet been defined and varies between centers and clinical protocols. To date, it has mainly been based on center-specific experiences and often each single patient received an individualized protocol. Harmonization is urgently needed to improve evidence regarding these treatments. However, personalized approaches based on prior therapy, pre-existing disease burden and responsiveness to single agents, are important considerations in the management of patients. Potentially high rates of prior organ toxicities in this heavily pre-treated and often refractory patient population have further diversified bridging therapy.[9] In this guidance, we try to balance the need for harmonization with the requirement of personalized approaches.

A growing number of reports emphasize the importance of bridging therapy across different age groups.[10] Recent data have highlighted that a lower disease burden at the time of CAR T-cell infusion correlates with improved long-term survival.[11,12] The beneficial effect of low disease burden may be a result of disease biology or a result of effective bridging therapy. In addition, high disease burden is associated with increased treatment-related complications, such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[13,14] Patients may therefore benefit from an effective reduction in disease burden prior to CAR T-cell therapy. However, recent studies in adults and smaller pediatric cohorts have shown that high-intensity bridging chemotherapy is associated with an increased incidence of infectious complications without improving long-term outcomes.[9,15,16] Compared to bridging prior to allogeneic hematopoietic stem cell transplantation (HSCT), in which studies on prognostic parameters for outcome have been conducted over decades,[17,18] the evidence for bridging before CAR T-cell therapy is sparse and inconsistent. Future prospective trials will need to demonstrate the relevance of minimal residual disease (MRD) and other prognostic parameters for outcome after CAR T-cell therapy.

In this report, we review bridging treatment strategies and clinical outcomes in children and young adults with R/R B-ALL treated with CD19-specific CAR T cells, and define consensus statements to harmonize approaches in the future. There will be no "one size fits all" in bridging therapy, but steps towards harmonization will strengthen the analysis of registry data, improve evidence and enable subsequent prospective clinical trials.

Methods

In a collaborative effort of pediatric and adult hematologists, we summarize current knowledge with the aim of establishing guidance for bridging therapy, as a step towards cross-institutional harmonization of such therapy. The guidance text is written with the aim of enabling better comparability of clinical data and increasing the level of evidence for the treatment of children and young adults with R/R B-lineage ALL until they can receive CAR T-cell infusion.

The methodological approach used to prepare this guidance and to reach a consensus included several steps. First, approved centers for CAR T-cell therapies in Austria, Switzerland and Germany were contacted and asked to participate in a process leading to the guidance. Second, a consensus workshop was organized to discuss aspects of treatment for different patient subgroups, the advantages and disadvantages of low-intensity and high-intensity

regimens, personalized *versus* uniform strategies, timing of approaches and the potential impact of bridging therapy on outcome after CAR T-cell infusion. A systematic literature search was performed before and after the workshop using PubMed. The levels of evidence were classified according to the National Cancer Institute's definitions, as shown in Table 1. The results of the workshop were shared in writing among the co-authors to reach a consensus wording.

Aims of bridging therapy

A major aim of bridging therapy is to control leukemia burden until the lymphodepletion prior to CAR T-cell infusion. To date, there are not enough conclusive results from prospective clinical trials to clearly define the aim of bridging therapy with regard to long-term outcome. However, an increasing number of non-randomized, controlled clinical trials and large, real-world, registry studies have provided data to make recommendations. High tumor burden has been shown to be associated with an increased risk of cytokine release syndrome.[13,14,19] In addition, several phase II trials and recent real-world data have shown that morphological remission (<5% blasts in the bone marrow) is associated with a significantly improved outcome in terms of event-free survival and overall survival.[12] In comparison

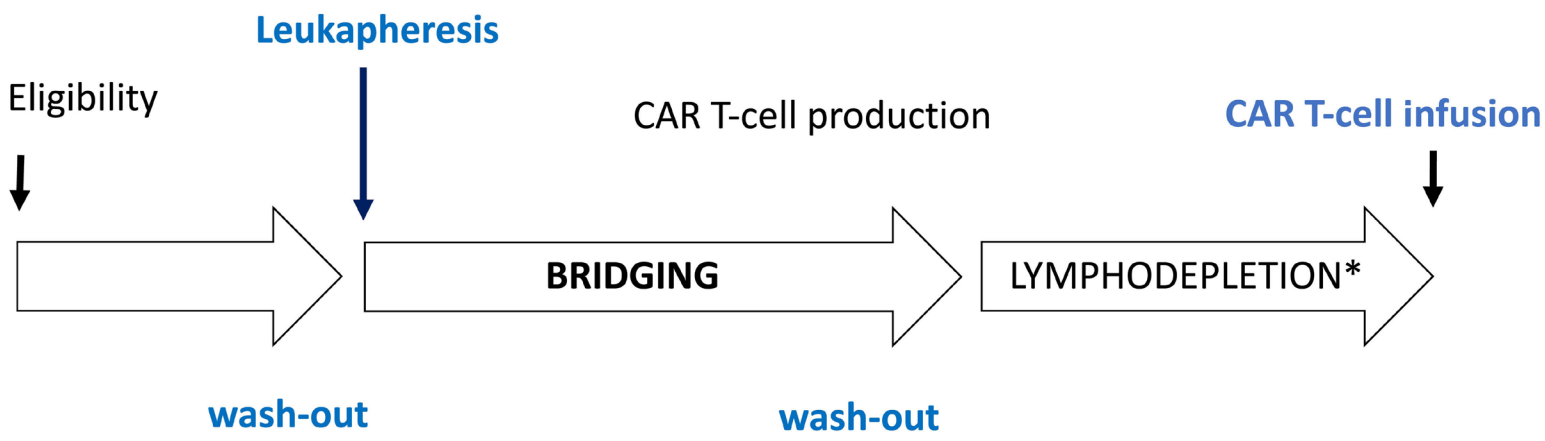

Figure 1. In the context of chimeric antigen receptor T-cell treatment, bridging therapy is usually considered as the phase between leukapheresis and the start of lymphodepleting therapy. The control of leukemia starts earlier, already prior to leukapheresis. However, treatment is subdivided into a first phase until leukapheresis and a bridging therapy phase until the start of lymphodepleting therapy and subsequent infusion of chimeric antigen receptor T cells. *The therapy used to achieve lymphodepletion has differed within and between different study protocols. A typical example of a lymphodepleting therapy contains fludarabine and cyclophosphamide. CAR: chimeric antigen receptor.

Table 1. National Cancer Institute's levels of evidence for adult and pediatric cancer treatment studies.*

Level of evidence	Definition
A1 Evidence	Randomized controlled clinical trial (double-blinded or non-blinded) with an endpoint of overall survival from a defined time, total mortality, or cause-specific mortality.
A2 Evidence	Meta-analysis of randomized controlled clinical trials with an endpoint of overall survival from a defined time, total mortality, or cause-specific mortality.
A3 Evidence	Randomized controlled clinical trial (double-blinded or non-blinded) with an endpoint of quality of life that is well-collected, clinically meaningful, and carefully assessed.
B1 Evidence	Randomized controlled clinical trial (double-blinded or non-blinded) with an endpoint of event-free survival, disease-free survival, or progression-free survival differences.
B2 Evidence	Meta-analysis of randomized controlled clinical trials with an endpoint of event-free survival, disease-free survival, progression-free survival or carefully assessed quality of life.
B3 Evidence	Randomized controlled clinical trial (double-blinded or non-blinded) with an end point of tumor response rate or quality-of-life measurement that does not reach the level described in A3.
B4 Evidence	Non-randomized, multicenter, prospective, controlled clinical trial with a planned comparison of efficacy including an end point of overall survival from a defined time, total mortality, cause-specific mortality, carefully assessed quality of life, event-free survival, disease-free survival, progression-free survival, or tumor response differences.
C1 Evidence	Case series or other observational study design, including trials with non-consecutive cases, with an endpoint of overall survival from a defined time, total mortality, cause-specific mortality, or carefully assessed quality of life.
C2 Evidence	Case series or other observational study design, including trials with non-consecutive cases, with an endpoint of event-free survival, disease-free survival, or progression-free survival differences.
C3 Evidence	Case series or other observational study design, including trials with non-consecutive cases, with an endpoint of tumor response rate or quality-of-life measurement that does not reach the level described in A3.
D Evidence	Anecdotal experience or expert opinion.

*Drawn from: *https://www.cancer.gov/publications/pdq/levels-evidence/treatment#_70.*

Table 2. Chemotherapy regimens.

Treatment	Drugs
Low-intensity regimen	
VDA	Vincristine, dexamethasone (or prednisone), PEG-asparaginase
Maintenance	6-Mercaptopurine (daily), methotrexate (weekly, p.o.), ± hydroxyurea
VDC	Vincristine, dexamethasone (or prednisone), cytarabine 75 mg/m^2/day on 4 consecutive days
High-intensity regimen	
VDA plus …	VDA plus (one of the following) - an anthracycline (daunorubicin or idarubicin or other) or - cyclophosphamide or - etoposide or - i.v. methotrexate or - i.v. high-dose cytarabine
Thiotepa	Dexamethasone (or prednisone) plus thiotepa
Clofarabine	Dexamethasone (or prednisone) plus clofarabine
Immunotherapy	
Blinatumomab	Dosing according to the approved label is recommended. Dosing recommendations for adults may be considered in adolescents
Inotuzumab	Increasing evidence of efficacy is counterbalanced by B-cell aplasia
Others	Rituximab in the case of CD20 expression. Several other lineage-specific antibody treatments are in development
Targeted therapy	
BCL-2	Venetoclax, navitoclax
Based on individual genotype of blasts	Tyrosine kinase inhibitors in the case of Philadelphia chromosome-positive acute lymphoblastic leukemia (dasatinib, nilotinib, ponatinib)

PEG-asparaginase: pegylated asparaginase; p.o.: *per os*; i.v.: intravenous; BCL-2: B-cell lymphoma 2 protein family.

to allogeneic HSCT,[17,18] negative MRD status prior to CAR T-cell therapy has not yet been shown to improve long-term outcome compared to that in patients starting with morphological remission alone.[12] For patients who start bridging therapy with a low disease burden, the aim of therapy is prevention of disease progression or maintenance of low-burden disease.

Bridging therapy primarily aims at achieving a low leukemia burden (<5% blasts in bone marrow) before starting lymphodepletion without severe toxicity (Level of evidence: B4).

Timing and duration of bridging therapy

The start of bridging therapy is guided by the label of the CAR products, which usually requires cytomorphological evidence of relapse/non-remission and consecutive scheduling of apheresis. Starting bridging therapy in a situation of increasing MRD appears to be reasonable, but evidence is currently lacking. The duration of bridging therapy has historically depended on the time necessary to manufacture the CAR T cells. Manufacturing that included cryopreservation and shipping required roughly 6 weeks up to several months, whereas fresh manufacturing required 10-14 days. Recent improvement in manufacturing protocols have shortened these periods.[20,21] A short bridging therapy has been preferred based on data comparing one or two cycles of bridging, each approximately 4-6 weeks.[9] However, the balance between achieving remission (see above) and reducing the number of treatment cycles has not been clarified. Furthermore, the published preference for one cycle contains a potential bias, due to the selection of chemosensitive patients. Based on the limited data in the literature and expert recommendations, the authors suggest one cycle of bridging therapy if possible, a preferred duration of no more than two cycles, and an earlier discontinuation of bridging therapy if a remission is achieved.

The start of bridging therapy is defined by the label of the chimeric antigen receptor product (cytomorphological relapse/non-remission). The duration of bridging therapy should be as short as possible to achieve remission (preferably one cycle) and up to 12 weeks (Level of evidence: D).

Treatment prior to apheresis

Treatment to control leukemia prior to leukapheresis is usually not considered “bridging therapy”, although it is part of the window between the decision to plan a CAR T-cell treatment and the start of the lymphodepleting therapy. Treatment prior to apheresis is particularly challenging, as lymphotoxic agents should not harm T cells that will be used to generate the CAR T-cell product. The number and functionality of lymphocytes in peripheral blood may be

low due to leukemic growth that crowds out physiological hematopoiesis, as well as the consequence of the therapy itself. Ideally, any anti-leukemic therapy should be preceded by the collection of T cells to generate a CAR product with optimal T-cell expansion capacities.[22,23] This may be feasible even in the presence of overt relapse, although inadvertent B-cell transduction has been described as a rare event.[24]

Acceptance criteria for apheresis are defined in most protocols and include a threshold of peripheral blood T-cell counts >150-200/μL. In an analysis of more than 100 procedures (in patients aged 1-25 years), the median reported absolute lymphocyte count ranged from 142-6,944 cells/μL.[25] Although 21.6% had absolute lymphocyte counts less than 500 cells/μL, the mononuclear cell target was obtained in 100% of all apheresis harvests and T-lymphocyte collection efficiency was 83.4%, with minor adverse events occurring in only 9.8%.[25] Elevated blast counts in peripheral blood have been described to interfere with successful apheresis and CAR production,[26,27] although the association between high blasts counts and lower $CD3^+$ cell collection yields may be due to lower numbers of circulating T cells. The threshold of peripheral blasts, below which apheresis is acceptable, has yet to be defined. In such patients, apheresis can be planned after an initial cycle of cytoreductive treatments. If the T-cell count is too low or T-cell collection is not feasible, chemotherapy should be administered to debulk leukemia burden, with the aim of performing apheresis in an interval during bridging therapy.[28] The timing of therapy prior to apheresis must take into consideration the wash-out period of the applied regimen. Most protocols define an absolute lymphocyte count threshold >300-500/μL to achieve successful collection by processing three or four times the total blood volume. In some protocols an absolute lymphocyte count of 200/μL is also accepted. CD3 counts should be >150-200/μL, but >100/μL is also accepted. However, these pragmatic recommendations are mostly derived from unpublished local feasibility studies.

In cases in which a sufficient number of lymphocytes cannot be achieved for apheresis, or relapse occurs very early after HSCT, an allogeneic CAR product from a healthy donor is an emerging approach. Recent reports have described CAR production from the stem cell donor.[29] In the case of sufficient chimerism after HSCT, the CAR product would be infused into a syngeneic immune system. In a meta-analysis of 16 studies with 220 patients, the rate of graft-*versus*-host disease was found to be low.[30] However, no commercial product has been authorized yet. Preclinical research has also included the development of universal of-the-shelf allogeneic CAR T cells using advanced engineering approaches.[31] Initial clinical data showed that challenges to this approach still remain.[32] In all allogeneic CAR approaches, bridging therapy would start upfront from the day of eligibility to CAR T-cell therapy.

Apheresis should be performed as early as possible before or during bridging therapy. Wash-out of lymphotoxic agents must be considered. Currently used thresholds are either a CD3 cell count >150-200/μL or an absolute lymphocyte count >300-500/μL (Level of evidence: D).

Patient subgroups

Currently anti-CD19 CAR T cells are approved for R/R ALL. This includes a heterogeneous population with primary refractory disease, those in second relapse or beyond, and those who relapse after HSCT, as well as patients treated with different first-line protocols and patients who have received different numbers of prior lines of therapies. This heterogeneity raises the question of whether one single approach can be applied to all subgroups or whether each of these different subgroups requires a separate bridging regimen. Based on the available data, a harmonized approach could be recommended for most relapsed patients (Level of evidence: D), as the available reports do not support a strategy of different approaches in subgroups.[6,33] Furthermore, patients under 18 years of age (including infants) and those over 18 years of age could be treated with the same bridging therapy and do not require separate approaches. In Europe most younger adults with ALL receive Berlin-Frankfurt-Münster-like intensive initial treatment protocols, comparable to standard pediatric protocols in adolescents. In the USA, many centers use hyperCVAD as a backbone.[34] In elderly patients dosing is usually adjusted and the choice of bridging therapies may differ due to different pre-treatment toxicity profiles. Despite molecular heterogeneity in the disease cohort in terms of aggressiveness (e.g. *TCF3-PBX1*, *ETV6-RUNX1*), we have not been able to find evidence that specific molecular subgroups require different bridging approaches.

Exemptions from a harmonized bridging approach arise from several specific considerations. First, patients whose disease progresses under first-line therapy are unlikely to achieve a remission with a bridging regimen that uses the same elements of standard induction. In such patients, a higher-intensity regimen or second-line therapy with agents different from the previous line is reasonable. Second, patients who relapse within 100 days of HSCT are particularly vulnerable to hematologic toxicity and may require even more reduced low-intensity regimens.[35] Third, radiotherapy of extramedullary manifestations of relapsed ALL may be used for disease control.

Patients who relapse after stem cell transplantation or with second or later relapse can receive the same bridging regimen. Early relapse after hematopoietic stem cell transplantation may require dose reduction. Primary refractory disease requires a change of treatment line, potentially with escalation of intensity to control disease (Level of evidence: C3).

Low-intensity *versus* high-intensity regimens

Many patients with R/R ALL are heavily pre-treated and prevention of toxicity is a high priority. Therefore, low-intensity regimens have been preferred over high-intensity regimens as bridging therapy.[9] Patients receiving high-intensity regimens have a higher incidence of grade 3 or 4 infections and experience more toxicities than patients treated with low-intensity regimens. Furthermore, recent data have shown that results in MRD-negative patients are not superior to those in MRD-positive patients analyzed prior to the start of lymphodepletion.[12]

The distinction between low-intensity and high-intensity regimens has not been properly defined (Table 2). The term "low-intensity" refers to the combination of agents, not the dose and should not be confused with lower doses of single agents. Although this definition may be arbitrary and lacks sound evidence, we consider it a valuable pragmatic approach. For most regimens, there will be no controversy between high- and low-intensity, but the boundary between "high" and "low" remains difficult to define. Even with an identical regimen, patients with different sensitivities to chemotherapy may experience very different durations of cytopenia. Alternative definitions such as "number of drugs per cycle or per week" or other systems could be proposed, but they also lack validation in clinical studies. A low-intensity regimen contains cycles of steroids, vincristine and asparaginase. Other options include low-dose cytarabine (75-100 mg/m^2 on 4 consecutive days) and agents used as maintenance therapy (e.g., oral 6-mercaptopurine, methotrexate). Anthracyclines are not considered a first choice as part of a bridging therapy because of their high potential to cause toxicity. The number of lines of prior therapy should be reviewed as part of the history when considering the appropriate bridging therapy to initiate. In some primary refractory patients, the leukemia has already shown refractoriness to the above mentioned low-intensity regimens and requires more personalized approaches.

Asparaginase does not cause the cumulative organ toxicity often associated with conventional chemotherapy. This advantage is offset by its long *in vivo* activity against lymphocytes. As patients with R/R ALL are usually heavily pre-treated, asparaginase is an option for bridging therapy. According to the recommendation for tisagenlecleucel, as an example, pegylated asparaginase (peg-asparaginase) should be stopped at least 4 weeks before leukapheresis and also before CAR T-cell infusion.[36] Asparaginase is considered a potential component of low-intensity regimens, given the definition of low/high-intensity regimens mentioned above. However, it can also be associated with serious complications of coagulopathy, thrombosis, pancreatitis, allergy and liver toxicity which may pose a risk for CAR therapy. Recommendations on asparaginase are based on rational expert opinion only, as no controlled clinical trials are available yet.

If possible, one cycle of chemotherapy until chimeric antigen receptor T-cell administration should be preferred instead of two or more cycles to reduce the risk of serious infections. Morphological remission is pursued, but complete regeneration of healthy hematopoiesis is not mandatory. Chimeric antigen receptor T cells should be administered as soon as possible after disease control (Level of evidence: D).

Whenever possible, a low-intensity regimen should be preferred, such as a backbone with vincristine, dexamethasone or low-dose cytarabine. Recommendations for time intervals between different agents and leukapheresis/chimeric antigen receptor T-cell infusion should be considered (Level of evidence: D).

Administration of pegylated asparaginase during bridging therapy, with at least 4 weeks wash-out prior to chimeric antigen receptor T-cell therapy, could be considered given its low cumulative organ toxicity (Level of evidence: C3).

Considerations on personalized approaches to individual patients in the context of prior lines of therapy, prior toxicities and disease burden

Responsiveness to prior lines of therapy is important for the choice of bridging regimen, especially in patients with primary refractory disease. In patients with multiple relapses or relapse after HSCT, the number of prior lines of therapy has not yet been identified as a prognostic marker. Although no evidence is available from clinical studies, it appears obvious that patients with progressive disease under a certain regimen require a change of drug substances to achieve a remission.

Previous toxicities must be taken into account when choosing a bridging regimen (e.g., avoidance of vincristine in patients with severe neuropathy). Uncontrolled viral and fungal infections are contraindications to high-dose and prolonged steroid treatment. Prevention of prolonged neutropenia is already addressed by the recommendation of a low-intensity bridging regimen (see above). Severe organ dysfunction (kidney, liver and heart) requires individualized regimens, but case reports suggest that even these are not insurmountable challenges to a therapy aimed at disease control.[37]

Disease burden was thought to be a relevant marker for prognosis in the past but this has not been proven in recent studies.[9] However, "responsiveness to prior lines of therapy" appears to be more important; for example, in the case of steroid-responsive disease, high blast counts are usually manageable. Disease burden at the end of bridging therapy has been associated with significantly improved outcome (see above),[12] whereas disease burden at the start of bridging therapy has not yet been defined as a significant risk factor. Several reports have hypothesized that starting bridging already when there is MRD may lead to a beneficial outcome[38,39] but sound evidence is still lacking and bridging data are sparse.

A rational, personalized approach to bridging therapy should be guided by responsiveness to prior lines of therapy and by severe prior toxicities (Level of evidence: D).

Immunotherapy prior to chimeric antigen receptor T-cell therapy

Antibody-based immunotherapy in B-lineage ALL has been a tremendous success, but in bridging therapy it carries a potential risk that administration prior to CAR T-cell infusion may jeopardize the expansion of CAR T cells in the absence of the target antigen. Blinatumomab is a bispecific T-cell engager (BiTE) that links CD3 expressed on T cells with CD19 on B cells/B-ALL cells, leading to direct targeting and destruction of $CD19^+$ leukemia cells. In initial studies investigating anti-CD19 CAR T-cell therapies, a prior anti-CD19 immunotherapy such as blinatumomab was considered to be a risk factor for non-response to CAR T cells.[11] Meanwhile, recent registry data demonstrated similar event-free survival rates in patients who had or had not received prior blinatumomab treatment.[11] In contrast, in another study among 51 patients with R/R B-cell precursor ALL (median age, 17 years) infused with tisagenlecleucel after lymphodepletion, prior blinatumomab was associated with an increased cumulative incidence of relapse, and shorter event-free survival and overall survival.[19] Therefore, the role of blinatumomab prior to CAR T-cell therapy requires further investigation.

Patients with a history of CAR T-cell treatment showed still relevant (but lower) response rates to bridging therapy, second CAR T-cell infusions and/or HSCT in small case series, even when the same CAR product was used.[40] However, blinatumomab non-response and high disease burden were independently associated with worse relapse-free survival and event-free survival following CD19-CAR therapy. Furthermore, patients with diminished CD19 expression ($CD19^{dim}$) have a risk of immune escape and consecutive relapse rate is high.[11] In the case of high CD19 expression, blinatumomab can be given up to 4-6 weeks prior to CAR T-cell infusion. For a strong functional CAR T-cell response, recovery of $CD19^+$ cells should be present for *in vivo* CAR T-cell activation and expansion. Systematic data on the use of blinatumomab immediately prior to apheresis are not available. However, bi-specific T cell engagers such as blinatumomab can cause T-cell exhaustion and their impact on the functionality of the CAR T-cell product remains to be investigated.

Inotuzumab ozogamicin (InO) is an anti-CD22 antibody conjugated to the cytotoxic antibiotic calicheamicin. InO is approved for the treatment of a first or subsequent relapse of CD22-expressing B-ALL in adults. A landmark phase III randomized study demonstrated the superiority of InO over standard chemotherapy in R/R B-ALL.[41] In children and adolescents phase I and II studies have proven the value of InO, with impressive responses reported for R/R leukemia.[42-44] Several reports on the sequential use of InO and CAR T-cell infusion from Europe and the USA show similar outcomes compared to those in R/R patients who did not receive InO. Since the number of reported cases is still low and outcome often reflects severity of disease, the use of InO for bridging therapy appears feasible but its role remains to be clarified. Of note, the severe depletion of B-lineage lymphocytes through the administration of InO did not prevent later CAR T-cell expansion *in vivo*.[45-47]

Prior use of anti-B-cell-immunotherapy (e.g., blinatumomab) is not a contraindication to chimeric antigen receptor T-cell therapy. CD19 expression should be measured prior to chimeric antigen receptor T-cell administration (B4 Evidence). Sequential therapy with inotuzumab-ozogamicin and CD19 chimeric antigen receptors appears feasible, but controlled trials are needed to clarify the evidence on long-term efficacy (Level of evidence: C2).

Intrathecal therapy

CAR T cells have been shown to migrate into the cerebrospinal fluid.[13] However, active central nervous system (CNS) disease has been a contraindication to CD19 CAR T-cell therapy in clinical trials. In recent retrospective studies, CAR T cells were found to be initially effective even in cohorts with CNS disease, although a high incidence of subsequent CNS relapse has been reported.[48,49] Therefore, most approaches have included intrathecal chemotherapy until resolution of CNS disease. Intrathecal triple therapy with a combination of methotrexate, cytarabine and prednisolone was considered first choice in relapsed disease. Monotherapy or a combination of two agents has also been used in patients with R/R disease. A combination of steroids with cytarabine has been discussed, either because of prior irradiation of the CNS or because of the rationale that methotrexate prior to apheresis may damage T cells. At initial diagnosis of ALL, post-induction CNS prophylaxis with intrathecal triple therapy did not improve 5-year disease-free survival for children with high-risk B-ALL compared to intrathecal monotherapy with methotrexate.[50] In the absence of systematic data for R/R ALL, intrathecal triple therapy remains the standard of care for CNS prophylaxis in R/R ALL.

Intrathecal therapy against active disease should be continued until CNS remission, preferably twice weekly. CNS remission is achieved when two consecutive cerebrospinal fluid samples are negative for leukemic blasts. In cases without active CNS disease, prophylactic treatment with intrathecal chemotherapy is recommended at least every 2-4 weeks.

All patients with relapsed/refractory acute lymphoblastic leukemia should receive intrathecal chemotherapy prior to chimeric antigen receptor T-cell therapy. In cases of active central nervous system disease, intrathecal therapy should be continued (1-2 times per week) until central nervous system remission (2 consecutive negative cerebrospinal fluid samples). Intrathecal triple therapy with methotrexate, cytarabine and prednisolone is the first choice (Level of evidence: B4).

Molecular targeted therapy

Screening for druggable molecular targets in all patients with R/R malignancies has become routine in most centers. Therefore, combining conventional chemotherapy agents with molecularly targeted therapies is an obvious, rational goal. However, patient-specific druggable molecular targets beyond ABL-class mutations or Philadelphia chromosome (Ph)-like ALL are rare. In a multicenter, phase I study, the combination of chemotherapy with the BCL-2 inhibitor venetoclax and the BCL-XL/BCL-2 inhibitor navitoclax was well-tolerated and showed promising results in R/R B-ALL.[51] In relapsed Ph$^+$ B-ALL, leukemia cells should be first analyzed for the presence of ABL1 kinase domain mutations. Treatment decisions and choice of a tyrosine kinase inhibitors could then be based on these results. Dasatinib and nilotinib are both second-generation tyrosine kinase inhibitor that have shown activity against R/R Ph$^+$ ALL in early-phase clinical trials.[52,53] In addition, ponatinib is a third-generation tyrosine kinase inhibitor that also inhibits the T315I mutation seen in the ABL kinase domain.[54] Of note, the combination of chemotherapy with small molecules requires special awareness because of the increased risk of bone marrow toxicity with prolonged cytopenia and subsequent serious infections. As kinase inhibitors may have a potential impact on CAR T-cell activation and expansion, they should be washed out and caution is appropriate when using them continuously before and after CAR T-cell infusion.[55]

Targeted therapy could be used in addition to bridging after apheresis based on specific mutations in the individual patient but can lead to prolonged cytopenia (Level of evidence: C3).

Wash-out before chimeric antigen receptor T-cell infusion

Almost all drugs against ALL have relevant toxicity against healthy lymphocytes (on-target, off-tumor effect). In order to achieve production of sufficient, high-quality CAR T cells

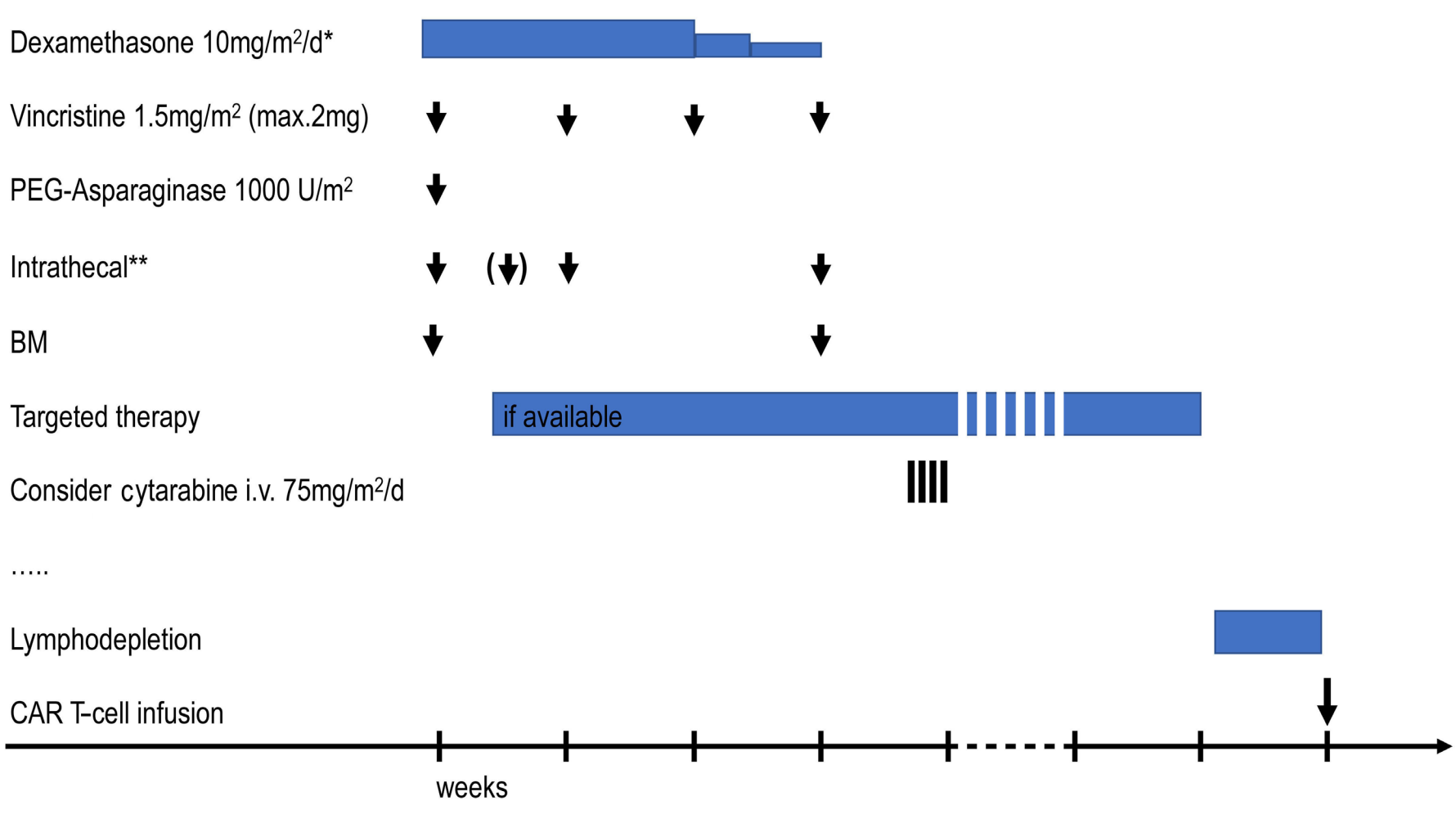

Figure 2. Backbone of a low-intensity bridging therapy before infusion of chimeric antigen receptor T cells. BM: bone marrow aspiration; CAR: chimeric antigen receptor.

which show optimal *in vivo* expansion, wash-out periods must be considered during bridging therapy. Based on the pharmacokinetics of the agents and small case series, an expert recommendation could be as follows: therapeutic systemic doses of steroids should be stopped >72 hours prior to CAR T-cell infusion (physiological replacement of hydrocortisone is continued if necessary). Medications with 6-thioguanine or intrathecal methotrexate should be stopped at least 1 week prior to CAR T-cell infusion. Anthracyclines, cytarabine and methotrexate should be stopped at least 2 weeks prior to CAR T-cell infusion. Longer periods of cessation are required for asparaginase (see below), antibodies used as serotherapy in HSCT such as antithymocyte globulin or alemtuzumab and all chemotherapy that is particularly toxic to T cells. These T-cell lytic agents include clofarabine and others and should also be used with caution due to their long wash-out times before both apheresis and CAR T-cell infusion. Manuals for commercial CAR products recommend 8 weeks of wash-out. However, these recommendations are mainly based on reason or expert opinion and not on evidence from clinical trials.

Clinical trials

Patients with multiple relapses or those in whom multiple prior lines of therapies have failed need novel experimental therapies. In recent years several new agents, which are typically tested in early clinical trials targeting refractory disease, have been described. However, early clinical trials are often limited to the use of single-agent therapies. Due to extensive pre-treatment with combinatorial multidrug regimens, there is a relevant risk of non-response to monotherapy. The level of evidence for bridging therapy is generally limited due to the rarity of its use and the consequent small cohorts of patients. For this reason, enrollment in early clinical trials is strongly recommended. A careful balance between patients' safety and innovation is therefore essential.

Inclusion of patients in phase I/II studies is encouraged. Single-agent regimens for bridging chemotherapy are not recommended.

Conclusions

Currently, there are no evidence-based treatment recommendations available for bridging therapy in R/R ALL prior to CAR T-cell therapy. The level of evidence is not yet strong enough to define a single first-line bridging therapy. Here, we summarize the available data in order to harmonize the inconsistent approaches across centers with support at the level of expert recommendation and some B and C evidence. Although harmonization is needed, a single treatment regimen will not be applicable because individual patients present with a wide range of pre-treatments and different histories of responses to therapy. This guidance does not, therefore, define a "gold standard", but will help centers to improve the evidence for clinical decisions.

The first choice is one cycle of a low-intensity regimen to induce morphological remission, i.e., <5% blasts in the bone marrow. A backbone treatment may include vincristine, dexamethasone, and asparaginase plus targeted therapy if available (Figure 2). In the case of high CD19 expression, blinatumomab can be given up to 4-6 weeks prior to CAR T-cell infusion, to allow recovery of the $CD19^+$ cells that play a role in CAR T-cell activation and expansion. If relapse occurs within 100 days after HSCT, a significant dose reduction of chemotherapy is recommended. Inclusion in clinical studies is encouraged but single-agent bridging therapy is not recommended.

Overall, bridging therapy is an area with an urgent need for better evidence from clinical trials. Beyond conventional generation of evidence, novel approaches such as drug response profiling using functional precision oncology, may further improve the safety and efficacy profile for R/R patients. This includes testing patient-derived ALL blasts with drugs to identify vulnerabilities and novel combinations.[56] This guidance may help to streamline the diversity of approaches to a small number of rational regimens, enable improved analysis of registry data and support the set-up of prospective clinical trials. More evidence from clinical studies is needed in the future.

Themes and definitions

- Bridging therapy is defined as antileukemic treatment between leukapheresis and the start of lymphodepleting therapy prior to chimeric antigen receptor (CAR) T-cell infusion. Treatment prior to leukapheresis is considered separately in this report.
- Assessment of evidence level is based on the National Cancer Institute's levels of evidence for adult and pediatric cancer treatment studies and is described in detail in Table 1.
- The definition of relapse in relapsed/refractory (R/R) diseases is used in accordance with the labeling of CAR T-cell therapies: second or higher relapse and first relapse after hematopoietic stem cell transplantations (HSCT) are considered R/R acute lymphoblastic leukemia (ALL). First relapse without prior HSCT is currently not an in-label indication for CAR T-cell therapy and is therefore not included in the definition of R/R ALL.
- Primary refractory disease among R/R diseases is defined as non-remission after the end of consolidation therapy, as applied and defined in the current pediatric protocols of AIEOP-BFM, ALLtogether, COG and others. In protocols designed primarily for adults, non-remission at the end of first consolidation is defined as primary refractory disease, such as in GMALL protocols.

• The term "disease burden" is often used in the field of CAR T-cell therapy. However, there is no common definition in ALL. It usually refers to the percentage of blast cells in the bone marrow. The definitions for "high disease burden" range from ≥5% blasts,[12] or ≥40% [57] to ≥50% blasts[58] and "low disease burden" below these numbers, respectively. Some reports also consider the percentage of blasts in peripheral blood as "disease burden". The term is not specified for extramedullary disease.
• Remission of ALL is defined as <5% blasts on cytomorphological analysis of bone marrow aspirate smears.
• Minimal residual disease (MRD) in bone marrow is detected by either *IG/TCR* real-time polymerase chain reaction, fusion gene transcript assessment, next-generation sequencing, or flowcytometry as described elsewhere.[59] A detection threshold of at least 10^{-4} is currently required to define MRD negativity.
• Toxicity of chemotherapy and immunotherapy is graded according to the Common Terminology Criteria for Adverse Events version 5.0.[60]
• Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been observed following immunotherapies for cancer. CRS is associated with elevated circulating levels of inflammatory cytokines. The definition of CRS is based on widely used grading systems.[61,62]
• Immune effector cell-associated neurotoxicity syndrome (ICANS) may manifest as encephalopathy, tremor, seizures and headache. The definition of ICANS is based on published criteria.[63] The understanding of clinical risk factors and the pathophysiology of ICANS is rapidly improving.[64,65]
• This consensus statement discusses high-intensity and low-intensity bridging therapy. The intensity of bridging therapy is as variable as the number of different regimens that have been used. High-intensity has recently been defined as myelosuppression for >7 days.[9]

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Contributions

All authors participated in the consensus process. The manuscript was written by TF and reviewed by all authors.

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Data-sharing statement

On request to the corresponding author, the authors are willing to make the original data and protocols of the guidance process available to other investigators without unreasonable restrictions.

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