

Role of allogeneic haematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukaemia in the era of immunotherapy

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the standard of care for adult acute lymphoblastic leukemia (ALL) patients. In recent years, with the continuous development of immunotherapy, such as chimeric antigen receptor T cells, blinatumomab, and inotuzumab ozogamicin, a series of vital clinical studies have confirmed its high response rate and favorable outcomes for ALL. Although the emergence of immunotherapy has expanded relapsed or refractory (r/r) ALL patients' opportunities to receive allo-HSCT, allo-HSCT is associated with potential challenges. In this review, the role of allo-HSCT in the treatment of adult ALL in the era of immunotherapy will be discussed.

Keywords: Acute lymphoblastic leukemia; Allogeneic hematopoietic stem cell transplantation; Immunotherapy; Chimeric antigen receptor-T cells

Introduction

Acute lymphoblastic leukemia (ALL) is a kind of malignant disease derived from hematologic stem cells. Intensive induction/consolidation chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the standard of care (SOC) for adult patients. Recently, several new immunotherapies have shown promising efficacy for relapsed or refractory (r/r) ALL patients in early-phase clinical trials. For example, blinatumomab, a bispecific T-cell-engaging (BiTE) antibody against CD19, and inotuzumab ozogamicin (InO), an anti-CD22 antibody drug conjugate (ADC), both demonstrated promising remission rates in ALL. Chimeric antigen receptor (CAR)-T cells, which constitute an immunotherapy featuring adoptive transfer of genetically modified effector T cells, show a high response rate of up to 73% to 83% and can even achieve long-term control of r/r ALL. In 2017, the Food and Drug Administration (FDA) approved CD19 CAR-T cell therapy for the treatment of r/r B-cell acute lymphocytic leukemia (B-ALL) and large B-cell lymphoma. Based on the outstanding outcomes in the treatment of r/r ALL, immunotherapies are believed to have broad prospects in the next 5 years. Could immunotherapies rewrite the guidelines of standard

treatment for ALL or eventually replace transplantation as the first-line treatment for ALL? In this review, we discuss the role of allo-HSCT in the treatment of ALL in the era of immunotherapy and the opportunities and challenges associated with allo-HSCT.

Allo-HSCT remains the SOC for ALL in the era of immunotherapy

Matched sibling allogeneic transplantation is the first-line therapy for ALL

Allo-HSCT is an effective and widely used method to treat hematological malignancies.^[1,2] Since the 1990s, various prospective clinical trials with large sample sizes have validated the role of allo-HSCT in ALL. In a large multicentric trial (LALA87), Sebban *et al*^[3] compared the outcome of allo-hematopoietic stem cell transplantation (HSCT) with those of other post-remission therapies (chemotherapy or autologous transplantation). Patients with human leukocyte antigen (HLA)-identical sibling donors were assigned to the HSCT group, while the other

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patients constituted the control group. The outcomes of patients with high-risk ALL were better in the HSCT group than those in the control group, with 5-year overall survival (OS) rates of 44% *vs.* 20% and 5-year disease-free survival (DFS) rates of 39% *vs.* 14%. In the study of MRC UKALL XII/ECOG E2993, Goldstone *et al*^[4] evaluated the efficacy of allo-HSCT for adults with ALL and compared autologous transplantation with standard chemotherapy. For adults with standard-risk ALL, the greatest benefit was achieved in the matched sibling donor (MSD) allo-HSCT group for the first complete remission (CR1), and autologous transplantation was less effective than conventional consolidation/maintenance chemotherapy for ALL patients. In the era before imatinib, allo-HSCT was considered an effective method for Philadelphia chromosome-positive (Ph-positive) ALL patients. The results of the UKALLXII/ECOG 2993 trial showed the superiority of allo-HSCT over chemotherapy in Ph-positive ALL patients, with 5-year OS rates of 44% for patients who underwent sibling donor allo-HSCT and 19% for patients who received chemotherapy. Even in the era of imatinib, MSD allo-HSCT was still superior to tyrosine kinase inhibitor maintenance therapy for patients with Ph-positive ALL based on the results of a prospective randomized controlled study named GRAAPH-2003.^[5] Thus, imatinib did not impact the role of MSD allo-HSCT as a first-line treatment for ALL. Therefore, allo-HSCT is regarded as front-line therapy in the age of MSD-HSCT for adult ALL patients. According to the definition of the National Comprehensive Cancer Network (NCCN) 2021, allo-HSCT remains the SOC for adult Ph-positive ALL, high-risk Ph-negative ALL, and minimal residual disease (MRD)-positive Ph-negative ALL. However, clear discrepancies regarding MRD status were evident in both the NCCN guidelines and Chinese Society of Hematology guidelines. Lv *et al*^[6] reported that haploidentical (haplo)-HSCT was superior to chemotherapy in terms of a lower incidence of relapse (CIR) and improved leukemia-free survival (LFS) and OS in all enrolled CR1 patients. When stratified by MRD status, haplo-HSCT decreased the CIR in both subgroups (MRD+ *vs.* MRD-) and improved LFS and OS in the MRD+ group, while LFS and OS were comparable between haplo-HSCT and chemotherapy in the MRD- group. Thus, the Chinese Society of Hematology suggests that all adult ALL patients, regardless of MRD status, should be advised to receive allo-HSCT.^[7]

Haplo-allogeneic transplantation achieves significant progress in ALL and can be standard therapy for adult ALL

In the past two decades, breakthroughs have been achieved in haplo-HSCT with either granulocyte colony-stimulating factor (G-CSF) plus anti-thymocyte globulin (ATG)-based regimens with unmanipulated T-cell replete grafts invented by a Peking group in China^[8-10] or post-transplantation cyclophosphamide (PT/Cy) for tolerance induction.^[11-13] Can haplo-HSCT be used as the first-line treatment for ALL patients?

Yan *et al*^[14] confirmed that haplo-HSCT with G-CSF and ATG-based regimens was a better post-remission therapy in adults with standard-risk adult ALL in CR1 than chemotherapy alone. In a multicenter phase III study, Lv

et al^[6] reported that the 2-year CIR, LFS, and OS with haplo-HSCT were all better than those with adult chemotherapy for young patients with standard-risk Ph-negative ALL in CR1. A study conducted by Sun *et al*^[15] also confirmed that haplo-HSCT was superior to conventional consolidation/maintenance chemotherapy as post-remission therapy for high-risk adult ALL. The above studies indicate that unmanipulated haplo-HSCT with G-CSF and ATG is effective for the treatment of ALL. Can haplo-HSCT achieve the same or even a superior effect compare with MSD allo-HSCT? In a retrospective study, Chen *et al*^[16] demonstrated that haplo-HSCT for the treatment of Ph-positive ALL achieved promising long-term survival, which was comparable with that of MSD HSCT in the imatinib era. Han *et al*^[17] retrospectively demonstrated that the outcomes of haplo-HSCT were equivalent to those of MSD for adults with standard-risk ALL in CR1. In a phase III randomized study, Wang *et al*^[18] demonstrated that haplo-HSCT achieved outcomes similar to those of MSD-HSCT for Ph-negative high-risk ALL patients in CR1. A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT) evaluated haplo-HSCT and MSD transplants in patients with ALL. The outcomes of adult patients with ALL in CR receiving allo-HSCT from haplo-donors were not significantly different from those of patients receiving transplants from MSDs in terms of LFS, OS, and GvHD-free relapse-free survival.^[19] In a multicenter study in Southwest China, patients with haplo-HSCT had a lower recurrence rate than patients with MSD allo-HSCT, indicating that the effect of haplo-HSCT on Ph-positive ALL may be superior to that of MSD allo-HSCT.^[20] In addition, Guo *et al*^[21] identified stronger graft-versus-leukemia effects with haplo-allografts than with HLA-matched stem cell transplantation. These studies confirm that the outcome of haplo-HSCT with G-CSF and ATG-based regimens is equivalent to that of MSD-HSCT in ALL and that allo-HSCT is still the first choice for ALL patients.

A series of studies have confirmed that haplo-HSCT with a post-transplant cyclophosphamide regimen is a potentially curative treatment for ALL. Srour *et al*^[22] analyzed the outcomes of 109 consecutively treated high-risk adult ALL patients who received haplo-transplantation with post-transplant cyclophosphamide. Nonrelapse mortality, the relapse rate and DFS at 1 year post-transplant were 21%, 27%, and 51%, respectively. Malki and his colleagues compared the outcomes of 1461 adult patients with ALL after haplo-PTCy or matched unrelated donor (MUD) transplantation. The 3-year probabilities of OS were comparable, with rates of 44% and 51% in haplo-PTCy and MUD transplantation patients, respectively.^[23] Sanz *et al*^[24] retrospectively analyzed the outcomes of adult patients with ALL in CR1 who had received allo-HSCT with PTCy from MSDs (*n* = 78), MUDs (*n* = 94) and haplodonors (*n* = 297) registered in the EBMT database between 2010 and 2018. For haplo-HSCT, MUD, and MSD patients, the 2-year CIR and NRM were comparable. The LFS and OS for haplo, MUD, and MSD patients were 59%, 62%, and 51% and 66%, 69%, and 62%, respectively. Similarly, the above studies demonstrated that donor type did not significantly affect transplant

outcomes in patients with ALL receiving allo-HSCT and that allo-HSCT is the current SOC for ALL patients.

The application of haplo-HSCT is a growing trend for ALL in both China and other areas throughout the world. By 2019, the number of cases of haplo-HSCT for ALL increased to approximately 2300/year, accounting for 24% of total haplo-HSCT cases in China. In the USA, the number of haplo-HSCT for ALL cases increased from fewer than 50 cases in 2010 to >300 cases/year by 2019. Even in the contemporary era, when immunotherapy develops rapidly, significant progress has been achieved for CAR-T cell therapy, BiTE antibodies, and ADCs. According to both 2021 NCCN Guidelines for ALL and the Chinese Consensus for allo-HSCT, high-risk ALL patients (including Ph+ patients) were advised to receive allo-HSCT. For MRD status, allo-HSCT was recommended for ALL patients in CR1 with MRD+, while the Chinese Society of Hematology suggests that all adult ALL patients, regardless of MRD status, are advised to receive allo-HSCT.

Immunotherapy provides more opportunities for allo-HSCT

The outcome of relapsed/refractory ALL is poor

Although more than 80% of adult ALL patients can achieve CR with intensive induction chemotherapy, the problem is that adult patients have a high recurrence rate. An estimated 74% of adult ALL patients ultimately relapse within 18 months after diagnosis. The median OS after recurrence is merely 8.6 months, with a 3-year survival rate of 24%.^[25] The only established curative option for relapsed ALL is allo-HSCT. However, the CR rate of reinduction salvage chemotherapy is only 40%.^[26] Most patients with relapsed ALL cannot achieve CR and are not eligible for transplantation. Even though patients receive salvage transplantation, the prognosis is not optimistic.^[27,28] Currently, adult r/r ALL patients face a low CR rate and short survival. Therefore, new treatment regimens are urgently needed to achieve disease remission, prolong survival, and provide a bridge to transplantation.

Immunotherapy expands r/r ALL patients' opportunities to receive allo-HSCT

The increased availability of alternative donors, especially haplo-donors, has resulted in the rapid growth of allo-HSCT, which ushered in a new era of "everyone has a donor." All adult ALL patients are recommended to receive allo-HSCT once they achieve CR based on the Chinese Consensus for allo-HSCT. However, most r/r ALL patients cannot achieve CR and thus lose their opportunity for allo-HSCT. With the development of immunotherapy, this problem may be solved. A series of clinical studies have demonstrated that approved CAR-T cell therapy has a favorable response rate in r/r ALL. In a single-center phase I-IIa study by Grupp *et al* in 2014, a total of 30 children and adults received the anti-CD19 CAR-T cell therapy tisagenlecleucel (CTL-019, Kymriah), and CR was achieved in 27 patients (90%).^[29] Later, in 2018, Grupp *et al* reported a phase II, single-cohort, 25-center, global study of tisagenlecleucel in pediatric and young adult

patients with CD19+ r/r B-ALL. The overall remission rate within 3 months was 81%.^[30] Studies from other centers have also demonstrated the best CR rates in r/r B-ALL after tisagenlecleucel treatment, which ranged from 67% to 93%.^[29-32] Fry *et al*^[32] reported that for patients with B-ALL who relapsed after receiving CD19 CAR-T cell therapy and were treated with CD22 CAR-T cell therapy, the CR rate reached 73%, and the median remission time was 6 months. CAR-T cell therapy also showed long-term survival in the treatment of r/r ALL. Shah *et al*^[33] reported the results of a phase II study named ZUMA-3, an international, multicenter, single-arm, open-label study evaluating the efficacy and safety of the autologous anti-CD19 CAR-T cell therapy KTE-X19 in adult patients with r/r B-precursor ALL; 71% of patients had CR or complete remission with incomplete hematological recovery (CRI), and the median durations of remission, relapse-free survival (RFS), and OS were 12.8, 11.6, and 18.2 months, respectively. For those who responded, the median OS was not reached, and 97% of them had MRD negativity. In China, CAR-T cell therapies in clinical trials have also shown very high remission rates. Hu *et al* reported that a total of 53 r/r B-ALL patients received split infusions of anti-CD19 CAR-T cells, and the overall 1-month remission rate of the 53 patients was 88.7%.^[34] Qian *et al* also observed that a total of 10 r/r ALL patients were treated with second-generation CD19 CAR-T cells, and six patients (60%) achieved CR.^[35] Therefore, considering its high remission rate and outstanding efficacy, CAR-T cell therapy offers a novel treatment option for r/r ALL. The current strategies for allo-HSCT in r/r ALL are as follows: with CAR-T cell infusion, r/r patients can achieve CR2 before transplantation and then bridge to allo-HSCT. The emergence of CAR-T cell therapy has expanded the opportunity for patients with r/r ALL to receive allo-HSCT and ultimately improved outcomes.

Blinatumomab is a bispecific T-cell engager antibody construct that directs CD3-positive cytotoxic T-cells to eradicate CD19-positive ALL blasts and has played a pivotal role in improving the outcomes of patients with r/r ALL.^[36] In a phase I clinical trial enrolling MRD-positive B-ALL patients, blinatumomab yielded a promising response regardless of MRD after chemotherapy.^[37] In a phase II trial enrolling r/r pre-B-ALL patients, blinatumomab improved the treatment efficacy significantly compared with standard therapy, with CR or CR with partial hematologic recovery (CRh) of 69% and mOS of 9.8 months.^[38] In another multicenter phase II trial that contributed to the FDA approval of blinatumomab to treat Ph-negative r/r pre-B-ALL, the CR rate was 32%, the median remission time was 6.7 months, and 31% of patients had an MRD-negative response, while the toxicity was controllable.^[39] Therefore, blinatumomab is a feasible and effective therapeutic option for r/r ALL. The emergence of blinatumomab gives more r/r ALL patients the opportunity to receive allo-HSCT.

Currently, the anti-CD22-targeted ADC InO is the most studied agent for r/r ALL.^[40] In a phase III clinical trial enrolling 326 r/r ALL patients, the experimental and control groups with 1:1 randomization received InO or standard care with intensive chemotherapy.^[41] The CR

rates in the InO and SOC groups were 80.7% and 29.4%, respectively. Patients in the InO group showed a significantly higher MRD-negative rate of 78.4% *vs.* 28.1% in the SOC group. Both the progress-free survival (PFS) and OS of the InO group were much longer than those of the SOC group, with a median PFS of 5.0 months and a median OS of 7.7 months compared with 1.8 and 6.7 months, respectively. Notably, InO significantly enhanced the remission rate of r/r ALL patients regardless of whether CD22 expression was above or below 90%. Consequently, InO provides more patients with disease control and is an effective treatment for r/r ALL; these patients can subsequently receive allo-HSCT to improve their prognosis. A table comparing the efficacies of each immunotherapy modality for r/r ALL is shown in [Table 1].

Bridging to allo-HSCT post immunotherapy significantly improves outcomes for r/r ALL patients

High recurrence rates were observed in many clinical trials when CAR-T cells were applied alone to treat r/r ALL, with rates of 21 to 45% in ALL adults and 21 to 67% in ALL children.^[29,32,42,43] Park *et al*^[42] revealed that patients with CAR-T cell infusion alone have short event-free survival (EFS) and OS in the long term, with median EFS and OS rates of 6.1 and 12.9 months, respectively. A study conducted by Huang *et al* also confirmed that although the CR rates are relatively high for relapsed patients after CAR-T cell therapy, the cumulative recurrence rate at 18 months was 68.3%, and the OS rate for CR patients was 30.0% at 18 months, with a median OS of 12.7 months,^[44] indicating that the long-term outcome of CAR-T cell therapy alone is unsatisfactory. However, some viewpoints suggest that certain ALL patients who are MRD negative after CAR-T cell therapy may not need to be bridged to allo-HSCT. The results from the Memorial Sloan Kettering Cancer Center showed that ALL patients with a low disease burden (<5% bone marrow blasts) before CAR-T cell treatment had markedly enhanced remission durations and survival, with a median EFS time of 10.6 months and a median OS time of 20.1 months,^[42] indicating that this is a controversial topic. In the future, if clinicians can distinguish patients who are prone to relapse from MRD-negative patients, for example, by screening out some biomarkers, not all MRD-negative patients need allo-HSCT. In addition, the survival rate of childhood ALL is higher, and perhaps in the future, children will not require bridging to allo-HSCT. However, a current trend for r/r adult ALL patients is to bridge to allo-HSCT once CR is achieved after CAR-T cell therapy.

A study from Peking University assessed the efficacy and safety of bridging CAR-T cell therapy to haplo-HSCT. Fifty-two patients with r/r Ph-negative B-ALL underwent haplo-HSCT after CAR-T cell therapy. After a median follow-up of 24.6 months, the 2-year probabilities of EFS, OS, and CIR were 76.0%, 84.3%, and 19.7%, respectively.^[45] In a clinical trial conducted by Lu Daopei Hospital, a total of 51 r/r ALL patients received CD19 CAR-T cell infusion, 90% of whom achieved CR or Cri; 27 CR/Cri patients then bridged to allo-HSCT, 85% of whom remained MRD negative with a median follow-up time

of 206 days, and 9 of 18 CR/Cri patients without allo-HSCT relapsed.^[46] In another study by Hu *et al*, 58 r/r B-ALL patients received split doses of CD19 CAR-T cells after lymphodepleting chemotherapy, and 51 (87.9%) patients achieved CR. Then, 21/47 MRD-negative CR patients bridged to allo-HSCT, while the remaining 26 patients did not receive HSCT. EFS and RFS were significantly prolonged by allo-HSCT.^[34] Recently, Shah *et al*^[47] examined the role of allo-HSCT following CD19 CAR-T cell therapy in improving long-term outcomes in 50 children and young adults (CAYAs). Thirty-one (62.0%) patients achieved CR, 28 (90.3%) of whom were MRD-negative. After a median follow-up of 4.8 years, the median OS was 10.5 months, and 21 of 28 (75.0%) patients achieved MRD-negative CR after receiving allo-HSCT. For those who received allo-HSCT, the median OS was 70.2 months. The CIR after allo-HSCT was 9.5% at 24 months; the 5-year EFS following allo-HSCT was 61.9%. To comprehensively evaluate and compare the efficacy and safety of consolidative HSCT after CD19 CAR-T cell therapy with non-HSCT in the treatment of ALL, a systematic review and meta-analysis were conducted. The study screened a total of 3441 studies and identified 19 eligible studies with 690 patients. Among the patients who achieved CR after CD19 CAR-T cell therapy, consolidative HSCT was beneficial for OS, the relapse rate, and LFS. For patients who achieved MRD-negative CR after CD19 CAR-T cell therapy, consolidative allo-HSCT was beneficial for OS, the relapse rate, and LFS.^[48] Thus, CAR-T cell therapy creates an opportunity for more r/r ALL patients to access allo-HSCT. On the other hand, bridging to allo-HSCT may be a safe and effective treatment strategy to improve EFS and OS after CAR-T cell therapy. A table comparing the outcomes of CAR-T cells alone *vs.* CAR-T cells followed by allo-HSCT is shown in [Table 2].

While remission rates of r/r ALL patients treated with blinatumomab have improved compared to those with conventional chemotherapies, remission is not durable when blinatumomab is used alone. The median duration of remission ranges from 4.6 to 7.3 months according to different clinical studies.^[36,41] Bridging to allo-HSCT after blinatumomab may overcome the short duration of remission and improve outcomes. Badar *et al*^[49] reported a real-world study in which 106 (47%) patients received allo-HSCT post blinatumomab treatment. Consolidation therapy with allo-HSCT after blinatumomab showed favorable prognostic significance, with PFS and OS rates at 2 years post allo-HSCT of 48% and 58%, respectively,^[50] suggesting that allo-HSCT may improve outcomes post blinatumomab therapy for patients with r/r ALL.

Similar to CAR-T cell therapy and blinatumomab, the short duration of remission without bridging to allo-HSCT post InO complicates its use as the ultimate treatment for r/r ALL. The INO-VATE clinical trial revealed that the median OS was only 7.7 months in the InO group, with a 2-year OS rate of 22.%.^[51] Fujishima *et al*^[52] reported that the median OS for InO arms was 5.8 months in r/r ALL patients. Bridging to allo-HSCT after InO may improve long-term outcomes. Marks *et al*^[53] investigated the role of allo-HSCT after remission in the setting of InO

Table 1: A comparison of the efficacies between each immunotherapy modalities for r/r ALL.

Studies	Number in treatment arm (N)	Immunotherapy modalities/target	Patients type	Prior HSCT	Response rate	MRD-CR rate	Long-term survival
TOWER (NCT02013167) ^[36]	271	Blinatumomab/ CD19	≥18 years with heavily pre-treated BCP ALL	34.7%	CR 33.6%, CRh 8.9%, CRi 1.5%, CR+CRh+CRi 43.9%	/	mOS: 7.7 months EFS (6 months): 31.0% DOR for CR/CRp/CRi: 7.3 months
MT103-211 (NCT02003612) ^[62]	189	Blinatumomab/ CD19	Adults with B-precursor Ph-negative r/r ALL	33.9%	CR/CRh 49.3%	/	OS (6 months): 57.6%, OS (12 months): 39.0%
INO-VATE (NCT01564784) ^[51]	164	InO/CD22	≥18 with R/R CD22+ BCP ALL, and were scheduled to receive their first or second salvage treatment. Ph+ patients were eligible if treatment with one or more second-generation BCR-ABL TKIs had failed	17.7%	CR/CRi 73.8%	70.7% (87/123)	mOS: 7.7 months, DOR and PFS for CR/CRi: 5.4 months and 5.0 months
NCT02000427 ^[63,64]	45	Blinatumomab/ CD19	Ph+ ALL who were r/r to at least 1 second-generation TKI	44.0%	CR 31.0%, CRh 4.0%, CRi 4.0%	88.0% (14/16)	mRFS: 6.8 months; mOS: 9.0 months
MT103-205 (NCT01471782) ^[65,66]	70	Blinatumomab/ CD19	Pediatric patients with r/r BCP-ALL	57.0%	CR 38.6% (27/70)	52.0% (14/27)	mOS: 7.5 months
ELIANA NCT02228096 ^[30]	75	Tisagenlecleucel KYMRIA CD19-CART	Pediatric and young adults with r/r	61.0%	81.0%	100.0% for CR	6 months EFS and OS rate: 73.0% and 90.0%; 12 months EFS and OS rate: 50.0% and 76.0%
NCT02975687 ^[67]	20 for infused; 22 for ITT	CNCT19 CD19-CART	Pediatric and adult B-ALL patients with r/r B-ALL	/	18 (90.0%) for infused 18 (82.0%) for ITT	100.0% for CR	mOS 12.91 months for N=20 infused mPFS 6.93 months for N=20 infused
NCT02315612 ^[32]	21	CNCT19 CD19-CART	r/r B-ALL treated children and adults, including 17 who were previously treated with CD19-directed immunotherapy	100.0%	12/21 (57.0%)	9/12 (75.0%)	Median remission duration: 6 months
NCT01044069 ^[42]	83 enrolled; 53 treated	CD22-CAR T	Adult patients with r/r B-ALL	100.0%	CR 44/53 (83%)	32/44	mEFS 6.1 months for N=53 treated, 12.5 months for CR; mOS 12.9 months for treated, 20.7 months for CR
ChiCTR-ONC-17013648 ^[55]	32 enrolled 27 infused CD19 CART, then 21 infused CD22 CART	CD19 CART and CD22 CART	Relapsed B-ALL after allo-HSCT	100.0%	23/27 (85.0%)	/	OS and EFS rate at 12 months and 18 months for N=27: 84.0% and 84.0%; OS and EFS rate at 12 months and 18 months for N=21 infused with CD19 and CD22: 67.5% and 67.5%
ZUMA-3 NCT02614066 ^[68]	54 enrolled 45 infused	KTE-X19, CD19 CART	Adult r/r B-ALL	13/45 (29.0%)	CR 53.0% (24/45), CRi 16.0% (7/45), CR/CRi 69.0% (31/45)	100.0% (31/31)	mDOR: 14.5 months, mRFS: 7.3 months, mOS: 12.1 months
NCT03389035 ^[69]	13 4 pediatric and 9 adult patients infused	CD19 CAR T	B-ALL patients relapsed after allo-HSCT	100.0%	CR 7, CRi 1, CR/CRi 8/13 (61.5%)	75.0% (6/8)	/
ChiCTR1900025419 ^[70]	9	CD19 CAR-T	Relapsed B-ALL post allo-HSCT	100.0%	100.0%	100.0%	mLFS: 18.1 months, mOS (2 years): 87.5%, mOS (2.5 years): 52.5%

ALL: Acute lymphoblastic leukemia; allo-HSCT: Allogeneic hematopoietic stem cell transplantation; B-ALL: B-cell acute lymphoblastic leukemia; BCP: B-cell precursor; CART: Chimeric antigen receptor T; CR: Complete remission; CRi: Complete remission with incomplete hematologic recovery; CRh: Complete remission with partial hematologic recovery; DOR: Duration of response; EFS: Event-free survival; HSCT: Hematopoietic stem cell transplantation; InO: Inotuzumab ozogamicin; ITT: Intention-to-treat; LFS: Leukemia-free survival; MRD: Minimal residual disease; OS: Overall survival; PFS: Progress-free survival; r/r: Relapsed or refractory; RFS: Relapse-free survival; TKI: Tyrosine kinase inhibitor; /:No data.

Table 2: A comparison of the outcomes of CAR-T cells alone vs. CAR-T cells followed by allo-HSCT.

Studies	Number patients (treated/enrolled)	Age (Years)	Prior HSCT	Target/costimulatory domain	CR/CRi rate	MRD-CR rate	Long-term survival	Patient number and time for consolidative allo-HSCT	Relapse rate	Outcomes for those received consolidative HSCT	Outcomes for those without consolidative HSCT
NCT01044069 ^[42]	53/83	≥18	35.8% (19/53)	CD19/CD28	83.0% (44/53)	66.7% (32/48)	OS: median 12.9 months, EFS: median 6.1 months	Patient number: 50.0% (16/32) – MRD CR patients, time: 44–312 (median 74) days	50.0% (16/32) – CR MRD patients	Relapse rate 37.5% (6/16)	Relapse rate 62.5% (10/16)
NCT02028455 ^[71]	43/45	1.3–25.3	65.1% (28/43)	CD19/4-1BB	93.0% (40/43)	93.0% (40/43)	OS: 69.5% (12 months), EFS: 50.8% (12 months)	Patient number: 28.0% (11/40) – MRD CR patients, time: /	45.0% (18/40) – MRD CR patients	Relapse rate 18.1% (2/11)	Relapse rate 55.2% (16/29)
NCT02435849 ^[30]	75/92	3–23	61.3% (46/75)	CD19/4-1BB	81.3% (61/75)	81.3% (61/75)	OS: 90.0% (6 months), 76.0% (12 months), EFS: 73.0% (6 months), 50.0% (12 months), LFS: 80.0% (6 months), 59.0% (12 months)	Patient number: 13.1% (8/61) CR/CRi patients, time: within 6 months	36.1% (22/61) CR/CRi patients	Relapse rate 0.0% (0/4), four others with unknown status	Relapse rate 41.5% (22/53)
NCT01593696 ^[31]	20/20	5–27	35.0% (7/20)	CD19/CD28	70.0% (14/20)	60.0% (12/20)	OS: 51.6% after 9.7 months, EFS: 78.8% after 4.8 months	Patient number: 83.3% (10/12) – MRD CR patients, time: 45–82 (median 51) days	16.7% (2/12) – CR MRD patients	Relapse rate 0.0%, (0/10)	Relapse rate 100.0% (2/2)
ChiCTR-llh-16008711 ^[46]	51/51	2–68	/	CD19/4-1BB	91.8% (45/49)	87.8% (43/49)	OS: /, LFS: 81.3% (6 m) after HSCT	Patient number: 60.0% (27/45) CR/CRi patients, time: 35–293 (median 84) days	24.4% (11/45) CR/CRi patients	relapse rate 7.4% (2/27)	relapse rate 50.0% (9/18)
NCT01626495 and NCT0102 9366 ^[29]	30/30	5–60	60.0% (18/30)	CD19/4-1BB	90.0% (27/30)	73.3% (22/30)	OS: 78.0% (6 months), EFS: 67.0% (6 months)	Patient number: 11.1% (3/27) CR patients, time: /	25.9% (7/27) CR patients	Relapse rate 0.0% (0/3)	Relapse rate 29.2% (7/24)
NCT01865617 ^[72]	53/59	20–76	43.4% (23/53)	CD19/4-1BB	84.9% (45/53)	84.9% (45/53)	OS: median 20.0 months, EFS: median 7.6 months	Patient number: 40.0% (18/45) – CR MRD patients, time: 44–138 (median 70) days	48.9% (22/45) – CR MRD patients	Relapse rate 16.7% (3/18)	Relapse rate 70.4% (19/27)
9 NCT02965092 and NCT03366350 ^[34]	58/60	≤70	5.2% (3/58)	CD19/4-1BB	87.9% (51/58)	81.0% (47/58)	OS: median 16.1 months, 68.9% for OS (6 months), 61.1% for OS (12 months); EFS: median 7.3 months	Patient number: 44.7% (21/47) – MRD CR patients, time: 33–89 (median 44) days	38.3% (18/47) – CR MRD patients	Relapse rate 9.5% (2/21)	Relapse rate 61.5% (16/26)
NCT02772198 ^[73]	20/21	5–48	50.0% (10/20)	CD19/CD28	90.0% (18/20)	78.6% (11/14)	OS: 90.0% (12 months), EFS: 73.0% (12 months)	Patient number: 77.8% (14/18) CR patients, time: median 68 days	22.2% (4/18) CR patients	Relapse rate 14.3% (2/14)	Relapse rate 50.0% (2/4)
NCT03173417 ^[74]	110/115	2–61	14.5% (16/110)	CD19/4-1BB	92.7% (102/110)	87.3% (96/110)	OS: 63.9% (12 months), LFS: 57.9% (12 months)	Patient number: 73.5% (75/102) CR patients, 69 MRD-, 6 MRD+, time: 36–120 (median 63) days	22.5% (23/102) CR patients: 10.1% (7/69) MRD-CR allo-HSCT, 50.0% (3/6)MRD+ CR allo-HSCT, 48.1% (13/27) CRA-T alone patients	Relapse rate 13.3% (10/75)	Relapse rate 48.1% (13/27)
NCT02735291 ^[75]	47/51	3–72	9/47 (19.1%)	CD19/4-1BB	38/47 (80.9%)	97.4% (37/38)	mOS for N = 47: 415.0 days, 1 year OS for N = 47: 53.0%; mRFS for N = 47: 319.0 days; 1 year RFS for N = 47: 45.0%	Patient number: 26.3% (10/38) CR times/	/	allo-HSCT vs. no allo-HSCT: OS HR 0.187, P = 0.105; RFS HR 0.533, P = 0.285	
NCT02315612 ^[76]	58/64	4.4–30.6	67.2% (39/58)	CD22/4-1BB	70.2% (40/57 evaluable)	87.5% (35/40)	mOS for CR: 13.4 months, mRFS for CR: 6.0 months, mEFS for evaluable N = 57 3.2 months	14 participants: 1 MRD+, 13 MRD-; time: 72 days	75.0% (30/40) CR patients	Receipt of HSCT was favorably associated with OS (P = 0.09) and very favorably associated with RFS (P = 0.0083) and EFS (P = 0.016)	

allo-HSCT: Allogeneic hematopoietic stem cell transplantation; CART: Chimeric antigen receptor T; CR: Complete response; CRi: Complete remission with incomplete hematologic recovery; DOR: Duration of response; EFS: Event-free survival; HSCT: Hematopoietic stem cell transplantation; HR: High risk; LFS: Leukemia-free survival; MRD: Minimal residual disease; OS: Overall survival; PFS: Progress-free survival; r/r: Relapsed or refractory; RFS: Relapse-free survival; /:No data.

treatment for r/r ALL. Of 236 InO-treated patients, 101 (43%) patients proceeded to allo-HSCT. The median post-transplant OS was 9.2 months with a 2-year survival probability of 41%. Thus, InO followed by allo-HSCT may provide an optimal long-term survival benefit.

Immunotherapy can be used as a powerful means to treat/prevent post-transplant relapsed ALL

As a powerful means to treat or prevent relapse after allo-HSCT, CAR-T cell therapy can be used for patients with relapsed ALL, for patients who are MRD positive and for prophylactic infusion in patients with high-risk B-ALL. For patients with donor-type or recipient-type recurrence, the efficacy of CAR-T cell treatment may not be affected by chimerism post-transplant, and the clinical outcome may not be substantially different. Patients with poor hematopoietic reconstitution may have a high probability of failure to manufacture CAR-T cells, but CAR-T cell reinfusion may have no effect on efficacy. Peking University Institute of Hematology reported an MRD-negative CR rate as high as 83.3% by HSCT donor-derived CAR-T cell infusion in patients with relapsed B-ALL after haplo-HSCT.^[54] However, the long-term efficacy was unsatisfactory, with an OS rate of 30.0% at 18 months.^[44] Additional treatment must be optimized, including a second HSCT, to further improve long-term efficacy after CAR-T cell infusion. Liu *et al*^[55] combined CD19 and CD22 CAR-T cells to treat post-transplant relapsed B-ALL patients. Twenty-seven patients received the initial CD19 CAR-T cells, and 23 (85%) patients achieved CR. Subsequently, 21 of 27 patients received the secondary CD22 CAR-T cells, 14 patients remained in CR, and seven patients relapsed, two of whom died from disease progression; the OS and EFS rates were 88.5% and 67.5% at 18 months. This combination strategy of sequential CD19 and CD22 CAR-T cell therapy significantly improved the long-term survival of B-ALL patients who relapsed after transplantation. Moreover, donor lymphocyte infusion (DLI) has been widely used in the management of relapsed hematologic malignancies after allo-HSCT.^[56] As an effective method, CAR-T cell therapy can also be used to prevent relapse in adult ALL post transplantation. For example, Peking University Institute of Hematology confirmed that donor-derived CAR-T cell therapy was effective for patients who were MRD positive and showed no response to DLIs in B-ALL after haplo-HSCT, with an 83.33% MRD-negative remission rate; half of the patients are currently alive without leukemia.^[57] In a prospective clinical study carried out by the Peking University Institute of Hematology, the safety and efficacy of CAR T-cell therapy in 11 MRD-positive B-ALL patients after allo-HSCT were evaluated. All patients (100%) achieved MRD-negative remission after donor-derived CAR T-cell infusion, with DFS and OS rates of 65.6% and 100%, respectively. Fourteen of 21 (66.7%) patients achieved MRD remission following DLI therapy, which was significantly lower than that following CAR T-cell therapy, indicating that pre-emptive donor-derived anti-CD19 CAR T-cell infusion shows a promising antileukemia effect on preventing relapse in MRD-positive B-ALL after allo-HSCT.^[58] Zhang *et al*^[59] treated two patients

with high-risk B-ALL with preventive infusion of donor-derived CD19 CAR-T cells on days 60 and 61 after allo-HSCT. No CRS or GVHD developed, and CAR-T cells could continually be detected. The patients survived for 1 year and 6 months disease-free, respectively, indicating that prophylactic donor-derived CAR-T cell infusion is effective and safe in high-risk B-ALL after haplo-HSCT.

Taken together, as a novel treatment, CAR-T cell therapy expands r/r ALL patients' opportunities to receive allo-HSCT. At the same time, bridging to allo-HSCT can overcome the high recurrence rate after CAR-T cell therapy and may improve the prognosis for these patients. In addition, CAR-T cell therapy can also be used as a powerful means to prevent relapse. CAR-T cell therapy does not impact the role of transplantation as the first-line treatment but instead provides more opportunities for transplantation.

Immunotherapy introduces potential challenges for allo-HSCT

With the continuous development of immunotherapy, some vital clinical studies have confirmed its high response rate and favorable outcomes for ALL. Since allo-HSCT is still the primary treatment strategy for ALL, it is unlikely to elicit revision of the guidelines at present. However, in the era of immunotherapy, will this promising treatment pose challenges for transplantation in the future?

First, given that allo-HSCT following CD19 CAR-T cell therapy improves long-term outcomes in r/r ALL, with a median OS of 70.2 months and a 5-year EFS of 61.9%,^[47] will patients at standard risk (SR) with MRD negativity postpone allo-HSCT until disease relapse? CAR-T cell therapy can be used for these relapsed patients to achieve CR2 and then bridge to allo-HSCT to improve outcomes. However, these assumptions still need to be verified by large-scale clinical trials. Second, if CAR-T cell therapy rather than allo-HSCT is used for standard-risk MRD-positive patients, will long-term survival be achieved? Lu *et al*^[60] assessed the effectiveness of CD19 CAR-T cells in 14 MRD-positive B-ALL patients. Among them, 12 patients achieved MRD-negative remission after CAR-T cell infusion. At a median follow-up time of 647 days, the 2-year EFS in MRD-positive patients was 61.2%, and the 2-year OS was 78.6%, indicating that patients at SR with MRD positivity may also choose to receive CAR-T cell therapy instead of allo-HSCT. Thus, patients with Ph-negative standard-risk B-ALL may choose whether to receive allo-HSCT based on MRD status in the future. Finally, if CAR-T cells are used as the first-line treatment for newly diagnosed ALL, can long-term survival be achieved? Xu KL team applied humanized CD19 CAR-T cells as first-line treatment for two newly diagnosed B-ALL patients. These two patients were treated with CD19 CAR-T cells within 2 weeks after diagnosis and did not receive chemotherapy or transplantation. They both achieved CR after treatment, and the CR durations were 27 and 17 months, respectively.^[61] The results suggest the possibility of CAR-T cell therapy as a first-line treatment for newly diagnosed ALL, but large prospective clinical studies are

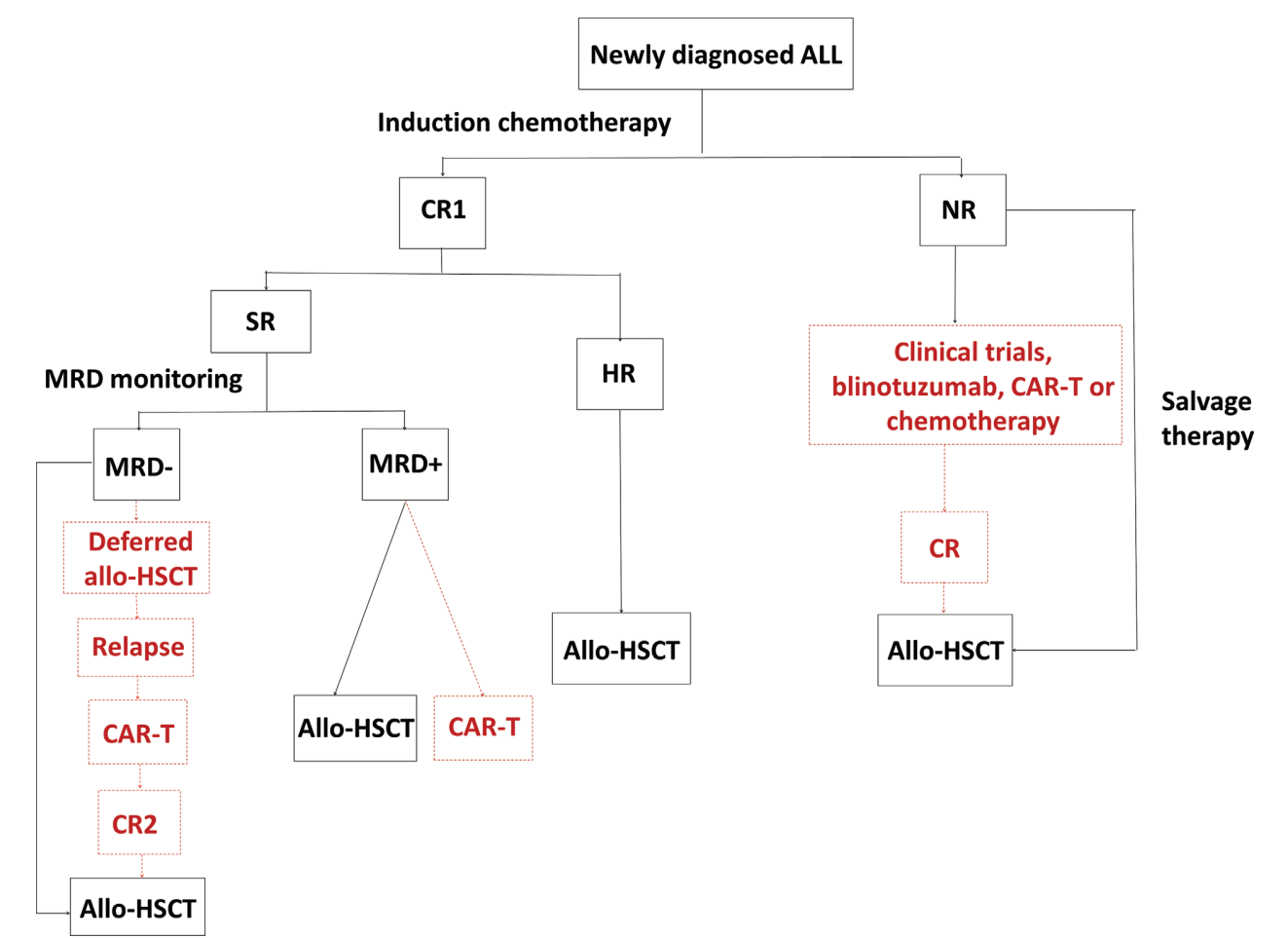


Figure 1: Flow diagram on clinicians may design a reasonable and affordable overall therapeutic protocol by integrating chemotherapy, the allo-HSCT and immunotherapy regimens. The black line flow chart represents the therapeutic protocol in the pre-immunotherapy era, whereas the red line flow chart represents the therapeutic protocol by integrating chemotherapy, the allo-HSCT and immunotherapy regimens in the era of immunotherapy. allo-HSCT: Allogeneic hematopoietic stem cell transplantation; CART: Chimeric antigen receptor T; CR: Complete remission; HSCT: Hematopoietic stem cell transplantation; HR: High risk; MRD: Minimal residual disease; NR: No remission; SR: Standard risk.

still needed to verify its efficacy. Therefore, in the near future, clinicians may design a reasonable and affordable overall therapeutic protocol by integrating chemotherapy, allo-HSCT and immunotherapy regimens for each individual according to their respective condition, including risk stratification and MRD status [Figure 1].

Conclusions

Allo-HSCT is still the most effective treatment for ALL even in the era of immunotherapy. Because of high remission rates and outstanding efficacy, immunotherapies such as CAR-T cells, blinatumomab, and InO offer novel treatment options for r/r ALL. The emergence of immunotherapy has resulted in more opportunities for patients with r/r ALL to receive allo-HSCT and finally achieve improved outcomes. The question of whether immunotherapy will replace allo-HSCT is unknown and may require time for verification. Currently, the superiority of allo-HSCT remains steadfast even in the era of immunotherapy.

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Conflicts of interest

None.

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