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Review Articles

Consensus on the monitoring, treatment, and prevention of leukaemia relapse after allogeneic haematopoietic stem cell transplantation in China: 2024 update

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A R T I C L E I N F O

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A B S T R A C T

The consensus in 2018 from The Chinese Society of Haematology (CSH) on the monitoring, treatment, and prevention of leukaemia relapse after allogeneic haematopoietic stem cell transplantation (HSCT) facilitated the standardization of clinical practices in China and progressive integration with the world. To integrate recent developments and further improve the consensus, a panel of experts from the CSH recently updated the following consensus: (1) integrate risk-adapted, measurable residual disease (MRD)-guided strategy on modified donor lymphocyte infusion (DLI) and interferon-α into total therapy, which was pioneered and refined by Chinese researchers; (2) provide additional evidence of the superiority of haploidentical HSCT (the dominant donor source in China) to matched HSCT for high-risk populations, especially for pre-HSCT MRD-positive patients; (3) support the rapid progress of techniques for MRD detection, such as next-generation sequencing (NGS) and leukaemia stem cell-based MRD detection; and (4) address the role of new targeted options in transplant settings. In conclusion, the establishment of a "total therapy" strategy represents a great step forward. We hope that the consensus updated by Chinese scholars will include the latest cutting-edge developments and inspire progress in post-HSCT relapse management.

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1. Introduction

Leukaemia relapse remains the major cause of death after Allogeneic haematopoietic stem cell transplantation (allo-HSCT) [1–8]. In recent years, targeted molecular agents and immune therapies have played crucial roles worldwide [9–15]. Nonetheless, based on disparities in allo-HSCT practices between China and the Western world, monitoring, prevention, and treatment for post-HSCT relapse in China [16] might not be in strict accordance with the current recommendations in the Western world. For example, in the era of targeted therapy (including cellular therapies, novel agents, and immunotherapeutic strategies) advocated by the National Cancer Institute (NCI) under the patronage of the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT), the modified donor lymphocyte infusion (DLI) system pioneered by Chinese scholars is still the backbone of relapse management after HSCT in China. Additionally, the difference between China and other countries in terms of donor population may involve better donor selection for patients at high risk of relapse, considering the potentially potent graft-versus-leukaemia (GVL) effect of haploidentical donors (HIDs). HIDs have been the largest source of allo-HSCT donors in China and have increased to more than 60 % since 2019 [1]; in contrast, HIDs accounted for 21 % (ranking second only to matched unrelated donors (URDs)) of the donor population according to Center for International Blood and Marrow Transplantation Registry (CIBMTR) data in 2023 [8]. Moreover, the focus of progress in measurable residual disease (MRD) monitoring was also somewhat different [17–20] including monitoring methods adopted and its integration into risk-adapted relapse management.

The following new developments have emerged since the establishment of the initial consensus [16]: (1) refinement of risk-adapted strategies on modified DLI and interferon-α (IFN-α) [21–26]; and the establishment of "total therapy", which includes allo-HSCT, MRD detection, and risk-stratified DLI with or without IFN-α [21–23]; (2) additional evidence of the superiority of haploidentical HSCT to matched HSCT for high-risk populations, especially for pre-HSCT MRD-positive patients [5,6,10]; (3) rapid progress in techniques for MRD detection, such as next-generation sequencing (NGS) and leukaemia stem cell (LSC)-based MRD detection [17–20]; and (4) an increasing number of studies addressing the role of new targeted options in transplant settings, including both nonimmunologic therapies, such as hypomethylating agents (HMA), venetoclax (B-cell lymphoma 2 inhibitors), FMS-like tyrosine kinase 3 (*FLT3*) inhibitors, and immunologic interventions, such as chimeric antigen receptor (CAR) T cells [11,27,28], blinatumomab and inotuzumab ozogamicin (INO).

Therefore, a panel of experts from the Chinese Society of Haematology (CSH) and the China International Exchange and Promotive Association for Medical and Health Care (CPAM) updated the recent advances since 2018, including **116** new references that focus on (1) new recommendations based on recent developments and (2) original recommendations supported by new evidence.

2. Methods

2.1. Composition of the panel

Twenty-two experts with recognized clinical and research expertise in allo-HSCT participated in the consensus discussion and were elected as members of the HSCT workgroup of the CSH. These experts represented the most active allo-HSCT centres (comprising approximately 60 % of total allo-HSCT cases) in China.

2.2. Scope of the review

A comprehensive computerized literature review of the PubMed database was conducted by the workgroup participants who served as the basis for the subsequent discussions. The HSCT workgroup of the CSH updated the recommendations from a consensus conference based on differences in post-HSCT relapse practices between China and the Western world [1,8].

Table 1
Diagnostic Methods to Monitor minimal Residual Disease after alloHSCT.

MFC	qPCR	NGS	dPCR
Advantages			
Sensitivity 10^{-3}-10^{-4}	Sensitivity 10^{-5}-10^{-6}	Sensitivity 10^{-3}-10^{-4}	Sensitivity 10^{-4}-10^{-6}
Availability >90 %	Frozen samples	Availability nearly 100 %	Availability nearly 70 %
Turnaround Fast (1–2days)	Low cost	Evaluation of clone evoluation	Absolute quantification
Low cost		Frozen samples	Frozen samples
Disadvantages			
Fresh cell only	Availability nearly 50 % for AML and 100 % for ALL	High cost	Turnaround Slow (3–5 days)
Antigen shift after treatments	Turnaround Slow (3–5 days)	High biological experts required	Specific assays for each molecular targets
Experts required	Specific assays for each molecular targets	Infuence by CHIP and germlines mutation	Less standardized
Inability of clone evoluation evaluation	Inability of clone evoluation evaluation	Turnaroud Very slow (10–21 days)	
Less standardized		Reliable markers not completely defined	
		Lowsensitivity due to sequencing errors unless correction methods included	

Abbreviation: MFC, multiparameter flow cytometry; qPCR, real-time quantitative polymerase chain reaction; dPCR, digital PCR; NGS, next-generation sequencing; AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia.

2.3. Formation of the consensus

The consensus has been updated using an iterative, multiple rounds, email-based approach–Delphi consensus protocols. The updated statements were sent to the expert panel. After three rounds of commenting and editing, the panel achieved at least 95 % consensus for the current recommendations. Recommendations were primarily based on retrospective analyses or cohort studies, collections of common practice data, and expert opinions of the committee members. Given the scarcity of high-quality evidence from randomized trials, recommendations were not graded.

3. Leukaemia relapse monitoring

Definition and classification of leukaemia relapse.

The definition of relapse is evolving due to the development of increasingly sensitive methods for the identification of MRD (see the next section), which can be divided into morphological relapse or MRD relapse according to the tumour burden [29,30]. Morphological relapse can also be categorized as intramedullary relapse, extramedullary relapse, or both [29].

a. Morphological relapse is defined as bone marrow blasts ≥5 %, the reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart, or the development of

Table 2
Criteria for residual disease positivity after allo-HSCT.

Biomarker for MRD	Techniques for MRD	Indications for intervention therapy	Ref.
WT1	qPCR	Two consecutive positive WT1 (0.6 % for adults and 0.8 % for children) with the interval of 10–14d[a]	4, 16
LAIP and DfN	MFC	Two consecutive positive MFC tests (with detectable residual disease) at a interval of 10-14d[a]	4, 16
BCR::ABL1	qPCR	i) without BCR::ABL1 transcripts converting to negative (less than 10-5) after HSCT; ii) with no decreasing trend in two consecutive positive tests (with the interval of at least 1 month); iii) conversion from negative to positive.	16, 91
RUNX1: RUNX1T1	qPCR	Less than 3 log compared with the baseline, or higher than 0.1 % after HSCT	19, 24, 42
CBFβ:MYH11	qPCR	Less than 3 log compared with the baseline, or higher than 0.1 % after HSCT	41
TLS::ERG	qPCR	Any levels of the gene detected are considered MRD-positive	16
E2A::PBX1	qPCR	Any levels of the gene detected are considered MRD-positive	16
SIL::TAL1	qPCR	Any levels of the gene detected are considered MRD-positive	16
ETV6:RUNX1	qPCR	Any levels of the gene detected are considered MRD-positive	16
SET::NUP214	qPCR	Any levels of the gene detected are considered MRD-positive	46
MLL rearrangement	qPCR	Any levels of the gene detected are considered MRD-positive	16
NUP98 rearrangement	qPCR	Any levels of the gene detected are considered MRD-positive	47
ZNF384 rearrangement	qPCR	Any levels of the gene detected are considered MRD-positive	48

Abbreviation: MRD = measurable residual disease; MFC = multiparameter flow cytometry; qPCR = real-time quantitative polymerase chain reaction; HSCT = haematopoietic stem cell transplantation.

[a] MRD positivity also include simultaneous WT1 and MFC positivity in the same sample.

extramedullary disease after complete remission (CR), CR with partial haematologic recovery (CRh) or CR with incomplete haematologic recovery (CRi) post-HSCT [30].

b. MRD relapse is defined as the conversion from MRD negativity to MRD positivity, indicated as an individual cut-off value or log reduction from the baseline level [30,31] (see criteria for MRD positivity below).

Currently, the two most extensively evaluated methodologies are multiparameter flow cytometry-based MRD (MFC-MRD) and molecular MRD (Mol-MRD), which are assessed by quantitative polymerase chain reaction (qPCR). Emerging exploratory technologies include next-generation sequencing (NGS) and digital PCR (dPCR).

3.1. Techniques for MRD monitoring

Integrated morphological, immunological, and molecular techniques have been applied to monitor leukaemia relapse [30–37] (Table 1). Here, we focused on MFC, qPCR, and NGS, which are methods that have rapidly developed in recent years in China while spectral cytometry, mass cytometry, dPCR, and single-cell RNA sequencing are under investigation for MRD detection and have not been routinely used in clinics in China. The Chinese Medical Association has summarized MRD monitoring after HSCT and recommended guidelines for specific diseases [33,34].

3.1.1. MFC

Traditional MFC-MRD detection is based on both leukaemia-associated aberrant immunophenotypes (LAIPs) and differences from normal (DfN) [30]. Although there are no standardized guidelines for panel design, the European LeukaemiaNet MRD Working Party recommends using cut-off values of 10^{-3} and 10^{-4} to distinguish MRD-positive patients from MRD-negative patients with acute myelocytic leukaemia (AML) [30,31,33] and acute lymphocytic leukaemia (ALL), respectively [32,34,38,39]. There are high incidences of false-positive and false-negative MRD tests in patients with acute leukaemia (AL), and the reasons for this have been identified [20]. Recent studies have shown the superiority of the $CD34^{+}CD38^{-}$cocktail^{+} LSC-based MRD assay, such as no apparent antigen shifts, higher sensitivity, and longer time from MRD positivity to haematologic relapse, to the traditional MFC method for outcome prediction in AML patients [18,40]. Thus, this method is advocated for residual disease detection despite it has not been adopted by European recommendations [30,31].

3.1.2. qPCR

PCR assays for MRD detection are based on the monitoring of clonal rearrangements of immunoglobulin or T-cell receptor genes as well as specific oncogenic fusion transcripts [19,41–48] and mutated or overexpressed genes [30]. Numerous studies have identified *wilm's tumor 1* (WT1) overexpression, a pan-leukaemia molecular target, as an additional MRD tool. The cut-off value and monitoring time point for WT1 positivity depend on different populations [49] and disease statuses [50].

3.1.3. NGS

NGS has been used in clinical trials, but not routinely for MRD detection in China [30,33,34], which is different from Europe practice [37]. Studies in B-ALL patients have indicated that NGS-based MRD assays targeting immunoglobulin genes are better at predicting relapse than MFC-MRD methods [51,52]. In contrast to NGS for MRD evaluation in ALL, the best combination of NGS target genes for AML MRD detection has not been well defined [30,53].

Each of the above mentioned MRD monitoring approaches has its own advantages and disadvantages (Table 1) [20]. Thus, MRD monitoring by at least two methods is warranted to inform suitable interventions to lower the risk of excess transplant-related mortality. Moreover, dPCR [54,55], mass cytometry [20], and novel microfluidic devices [56] are under investigation.

Recommendations: Leukaemia relapse monitoring.

Regular MRD monitoring with at least two modalities is crucial.

1 Criteria for MRD positivity (Table 2)

A. Leukaemia without specific fusion gene markers:

LAIP and DfN expression by MFC and/or WT1 overexpression by qPCR are often used as biological markers for MRD surveillance. The following criteria are adopted. At least one of the following criteria should be met between 2 months and 1 year after HSCT.

a. Two consecutive positive WT1 with an interval of 10~14 d; the cut-off value was defined as 0.6 % for adults and 0.8 % for children.
b. Two consecutive positive MFC tests with detectable residual disease at intervals of 10–14 d.
c. Simultaneous WT1 and MFC positivity in one sample.

B. Leukaemia with a specific fusion gene

a. Philadelphia chromosome-positive ALL: *BCR::ABL1* transcripts not converted to negative (less than 10^{-5}) after HSCT or converted from negative to positive (higher than 10^{-5}).
b. CBF-Leukaemia: <3-log reduction from the baseline and/or the loss of a ≥3-log reduction in the *RUNX1-RUNX1T1* transcripts; *CBFβ::MYH11/ABL1 gene level* higher than 10^{-3} (3-log reduction compared to baseline).

Table 3
Studies of CAR-T after allo-HSCT.

Author Ref. and year Number,n Follow-up	AML/MDS(n) Target	ALL (n) Target	Disease status	Cell source	Allo Donor (n)	CR (%)	Relapse after CR (%)	EFS/PFS (%)
Chen et al., 2020[68] N = 35 1.5-Year		35 CD19	relapse	Auto 20/Allo 15	MSD = 4 HID = 10 URD = 1	85.7	68.3	NA
Zhang et al., 2021[69] N = 43 1-Year		43 CD19	relapse	allo	MSD = 17 HID = 26	79	41	43
Luo et al., 2024[70] N = 15 1-Year		9 CD19	relapse	allo	MSD = 3 HID = 6	100	2/9	77.8
Tan et al., 2023[71] N = 43 2-Year		22 CD19 21 Con DLI	relapse	allo	MSD = 6 HID = 16	77.3 Con 61.5	NA	50.0 Con 4.8
Hua et al., 2021[72] N = 28		13 CD19 15 Con DLI	relapse	allo	MSD = 6 HID = 7	69.2 Con 26.7	NA	50.0 Con 4.8
Zhao et al., 2021[11] N = 33 1-year		12CD19 21 Con DLI	MRD+	allo	MSD = 4 HID = 8	100MRD-Con 66.7	42.8	65.6
Cui et al., 2021[73] N = 6	6 CD38		relapse	Auto 4/Allo 2	NA	66.7	50	6.4m
Ma et al., 2021[74] N = 6	2 CLL1		relapse	Auto 1/Allo 1	NA	100	0	8m,3m

Abbreviation: AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukaemia; Allo, allogeneic; auto, autologous; CR, complete remission; EFS, event-free survival; PFS, progression-free survival; MSD, matched sibling donor; HID, haploidentical donor; URD, unrelated donor; Con, control; DLI, donor lymphocyte infusion; MRD, measurable residual disease; NA, not analyzed.

c. KMT2A (*MLL)* rearrangement: KMT2A fusion gene/ABL1 greater than 10^{-5}
d. Other relatively rare fusion genes: genes with *TLS::ERG, E2A::PBX1, SIL::TAL1, ETV6::RUNX1, SET::NUP214, NUP98* and *ZNF384* rearrangement frequencies greater than 0.0 % were considered MRD positive.

4. Monitoring frequency and sample source

A. Frequency
   a. Bone marrow morphology, MRD, and chimeric status should be regularly detected at +1, +2, +3, +6, +9, +12, +18, +24, +36, +48, and +60 months after transplantation. Each centre can follow its own schedules according to the actual situation, increase the frequency of monitoring according to pre-HSCT risk assessment, adjust intervals according to previous tests, and adjust whenever progression is suspected.
   b. Patients with detectable MRD are recommended for a recheck within 2–4 weeks.
B. Sample source
   a. Once relapse occurs, the bone marrow morphology, immunophenotype, cytogenetics, molecular markers (MICM), chimaerism and HLA loss [57] should be tested when appropriate. Whenever possible, HLA loss testing is advocated at least in the setting of haploidentical HSCT.
   b. The detection of chimaerism can be performed using bone marrow (BM) and/or peripheral blood (PB) samples (sorted $CD34^+$ cells from PB when appropriate), with bone marrow testing shown to be more sensitive in some studies.
   c. Bone marrow samples are preferred for other MRD tests. Although PB has also been used to detect MRD in some studies from the Western world [31], few data are currently available from China comparing BM and PB samples for MRD detection.

5. Treatment and prevention of leukaemia relapse

Risk-adapted strategies for relapse management after allo-HSCT include treatment for morphological relapse, preemptive intervention for positive MRD after transplant, and prophylaxis for advanced leukaemia patients [4,16,21–26]. The modified DLI protocol was pioneered by Huang et al. in the last two decades [4,21–23]. This approach included the infusion of granulocyte-colony stimulating factor (G-CSF)-mobilized PB progenitor cells and the administration of short-term immunosuppressive (STI) agents for graft-versus-host disease (GVHD) prophylaxis after DLI, which is different from the EBMT DLI system [60]. The refinement of risk-directed modified DLI and IFN-α is still the backbone of relapse management [21–26] in the era of new targeted options, especially when considering the scarcity and economic burden of commercially available agents in China [36]. Total therapy is thus established, comprising allo-HSCT, MRD monitoring, and risk-directed DLI with or without IFN-α [21–23]. In addition, immune suppression (IS) withdrawal and a second transplant remain the classical methods although the number of second-HSCT is relatively small due to concept, culture, and affordability of Chinese population [58,59]. Finally, the management of post-HSCT relapse may require a multimodality strategy.

5.1. Treatment of morphological relapse

Currently, donor cell therapy remains the foundation of most approaches for inducing remission in leukaemia patients who relapse post-HSCT [21–23]. In addition, novel pharmacologic and cellular treatments have been successfully used to treat post-HSCT relapse [11,12].

5.1.1. Modified DLI for post-HSCT relapse treatment

Modified DLI, a novel transplant technique system pioneered by Huang et al. [4,21–24], markedly broadens the applicability of DLI even in haploidentical HSCT [60]. Since its first use, modified DLI (described above) has become the standard of care for post-HSCT adoptive immune strategies in China [16,21–23,61,62]. Details of the modified DLI system have been refined [21,61]. Briefly, the median dose of mononuclear cells (MNCs) for each infusion was 1.0×10^8/kg, with a median $CD3^+$ cell count of 3.0×10^7/kg. Patients could receive repeated DLIs every 1–3 months depending on MRD and GVHD status after each infusion (up to four courses of modified DLIs until 1 year after achieving CR). Patients receiving DLIs from HIDs received CSA for 6 weeks after each infusion to prevent GVHD. Subjects receiving DLIs from matched sibling donors (MSDs) received CSA or methotrexate (MTX) for 4 weeks after each infusion to prevent GVHD.

Adjunctive approaches to improve DLI, including chemotherapy before DLI, combination of novel targeted agents with DLI, and novel methods to enhance T-cell function or specificity, have been explored [62–66]. Genetic characteristics predict the response to venetoclax plus HMAs [63]. It was also suggested that the best survival was achieved with sorafenib-containing chemotherapy followed by DLI for *FLT3*-internal tandem duplications (ITD) patients who relapsed after allo-HSCT

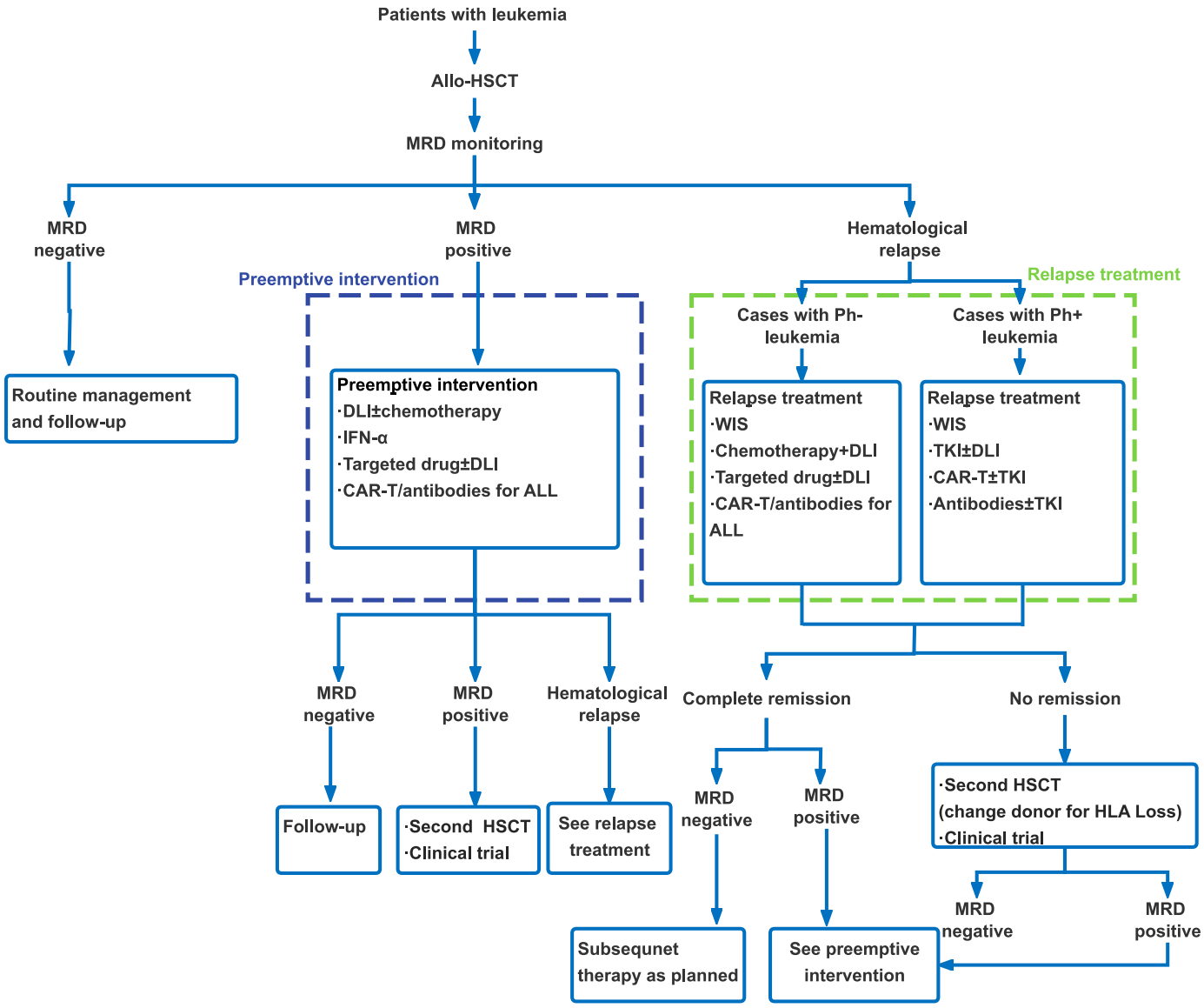

Fig. 1. Recommendation for preemptive therapy or treatment after allogeneic stem cell transplantation. For leukaemia patients with morphological relapse or MRD positivity after allogeneic HSCT, the combined use of available treatment options is recommended according to disease type.

[65].

5.1.2. Novel cellular therapies

CAR-T-cell therapy has emerged as a promising form of adoptive T-cell immunotherapy for selected haematologic malignancies. China has the largest number of registered CAR-T-cell trials [67] (Table 3).

Scholars at Peking University reported that 85.7 % of B-ALL patients who relapsed post-HSCT achieved MRD-negative CR after CAR-T-cell therapy, and the OS rate for patients who achieved CR was 30.0 % at 18 months [68]. Recent trials from China reported that donor-derived CD19 CAR-T-cell therapy is safe [69,70] and may be more effective than chemotherapy followed by DLI for B-ALL patients who relapse after allo-HSCT [71,72]. Additionally, efforts have been made to develop CAR-T cells, for post-HSCT AML relapse [73,74]. Altogether, taking full advantage of HSCT and CAR-T-cell therapy in the treatment of post-HSCT relapse is possible [75].

5.1.3. Novel pharmacological therapy

Salvage venetoclax combined with HMAs resulted in a CR/CRi incidence of 34.1 % for patients who experienced post-allo-HSCT relapse [76]. In addition, venetoclax, azacitidine, and homoharringtonine (VAH) are promising and well-tolerated regimens for R/R AML, including post-HSCT relapse [77], and sorafenib plus VAH is well tolerated and highly effective against R/R AML with *FLT3-ITD* [78]. Regarding immunologic agents, blinatumomab is a potential strategy for eradicating lymphoblastic cells for HLA loss relapse after haploidentical HSCT [79]. Researchers from abroad have demonstrated the safety and efficacy of blinatumomab or INO combined with DLI in treating post-HSCT ALL relapse [80].

5.1.4. Second allo-HSCT

The outcomes of the second transplant were similar to those of the DLI according to the EBMT studies [82]. Moreover, a second HSCT could be a salvage or consolidation option for patients who relapse after DLI or CAR-T-cell therapy [58,83]. Second HSCT with a different donor from the first HSCT did not result in a survival benefit except for patients with HLA loss [58,81]. Instead, the duration of CR after the first HSCT, disease status, HLA loss, physical condition, and donor intention can be helpful in determining the choice of donor and conditioning regimen [57,81–84]. Second-HSCT outcomes from Chinese reports are similar to or somewhat inferior to the EBMT data in more recent years, possibly due to the lower proportion of CR status at the time of second HSCT and

Table 4
Studies of pDLI (prophylactic (pro-DLI)/preemptive DLI (pre-DLI))after allo-HSCT.

Author Ref. and year Number,n Follow-up	Disease/marker		Int	Group			Relapse			NRM			LFS		
	AML/MDS Marker (n)	ALL marker (n)		DLI (+) (n)	MRD (+) DLI (−) Con (n)	MRD (−) DLI (−) Con (n)	DLI (+) (%)	MRD (+) DLI (−) Con (%)	MRD (−) DLI (−) Con(%)	DLI (+) (%)	MRD (+) DLI (−) Con (%)	MRD (−) DLI (−) Con(%)	DLI (+) (%)	MRD (+) DLI (−) Con (%)	MRD (−) DLI (−) Con(%)
Yan,et al., 2012[4] N = 814 3-Year[a]	*WT1* +LAIPs, (529)	*WT1* +LAIPs, (285)	Pre-DLI	56	49(IL-2)	709	27.8	64.4	18.1	14.0	11.4	19.7	55.6	24.1	61.6
Yuan,et al., 2021[96] N = 55 2-Year[b]	*WT1* +LAIPs >+100d, (41)	*WT1* +LAIPs, >+100d (14)	Pre-DLI	25	30 (IL-2)	NA	26.2	17.3	NA	5.5	3.3	NA	69.7	79.7	NA
Yang,et al., 2023[108]	*WT1* +LAIPs (177)	*WT1* +LAIPs, (90)	Pre-DLI	39	NA	NA	36.7	NA	NA	10.3	NA	NA	53.0	NA	NA
N = 271 3-Year[a]			Pro-DLI	95			25.3			11.3			63.4		
Wang et al., 2014[19] N = 92 2-Year[a]	*RUNX1-RUNX1T1,* (92)		Pre-DLI	17	13	62	24.0	87.0	NA	NA	NA	NA	64.0	0.0	NA
Fan et al., 2022[24] N = 16 2-Year[b]	*RUNX1-RUNX1T1,* (16)		Pre-DLI	16	88 (IFN)	NA	19.6	16.8	NA	20.1	3.6	NA	60.3	78.2	NA
Vipul Sheth et *al* 2021[87] N = 217 2-Year[a]	chimerism, (203)	chimerism, (14)	Pre-DLI	53 (36 response+17No-response)	52	111CC (complete chimerism)	MC(mixed chimerism) 38	NA	32	MC14	NA	25	MC45	NA	38.5
Yan,et al., 2022[23] N = 105 5-Year[a]	*105*		Pro-DLI	87	NA	18	27.6	NA	50.0	21.6	NA	33.3	50.8	NA	16.7
Wang et al., 2020[22] N = 932 3-Year[a]	631	301	Pro-DLI	297	NA	635	32	NA	45	20	NA	18	47	NA	36
Yang,et al., 2021[108] N = 175 5-Year[a]	36	32	Pro-DLI	34	NA	34	14.7	NA	49.3	14.8	NA	16.7	64.6	NA	33.9
Yu,et al., 2020[97] N = 251 3-Year[a]	*111*	115	Pro-DLI	199	NA	52	30	NA	43	NA	NA	NA	NA (DLI vs no LFS P < .001 HR = 0.042)	NA	NA

Abbreviation: AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukaemia; Int, intervention; DLI, donor lymphocyte infusion; MRD, minimal residual disease; Con, control; LAIPs, leukaemia-associated immunophenotypic patterns; MFC, multiparameter flow cytometry; WT1, Wilms' tumor gene 1; NA, not analyzed; NRM, non-relapse mortality; LFS, leukaemia-free survival; HR, hazard ratio; a, time after transplantation; b, time after DLI.

delayed interval from relapse to second HSCT [58,82,84].

Recommendations: Treatment of morphological relapse.

For leukaemia patients who relapse after allogeneic HSCT, the combined use of available treatment options is recommended (Fig. 1).

A. Patients with Ph-positive leukaemia
   a. TKI ± multiagent chemotherapy or TKI ± corticosteroid.The response of *BCR::ABL1* to TKIs and the mutation of ABL kinase are considered to determine the selection of TKI generation and chemotherapy. Subsequent DLI should be advocated after CR is achieved when there is no GVHD. The duration of TKI administration remains unclear. Tyrosine kinase inhibitors should be applied for at least 1 year if *BCR::ABL1* is continuously negative during therapy. If *BCR::ABL1* is persistently positive or converts from negative to positive during treatment, ABL kinase mutation should be tested to determine whether to change TKI, perform DLI or use novel agents.
   b. The use of blinatumomab ± TKI or INO ± TKI for Ph-positive ALL patients is one of the choices depending on the economic burden and physician decision.
   c. CAR-T-cell therapy for Ph-positive ALL is recommended.

B. For patients with AML, Ph-negative ALL or MDS
   a. Before starting treatment, MICM, chimaerism and HLA loss should be tested when appropriate.
   b. Chemotherapy followed by DLI is preferred for patients without HLA loss. The addition of targeted agents to chemotherapy regimens is recommended for patients with FLT3-positive leukaemia. The use of other novel agents or regimens is one of the choices depending on the use of molecular markers, economic burden and physician decision. The infused cell dose of DLI should include the donor type, timing and frequency of DLIs, and previous history of GVHD. For modified DLIs, the $CD3^+$ cell dose is approximately 3×10^7/kg. GVHD prophylaxis is given to patients receiving DLIs from HIDs or MSDs for 6 or 4 weeks after each infusion, respectively. MRD- and GVHD-directed multiple modified DLIs can further improve outcomes: consolidation DLIs are given at 3, 6, and 9 months after the first infusion with a negative MRD test and no GVHD, while delayed consolidation DLIs to 4–6 months after GVHD are resolved for patients with a negative MRD test but who have GVHD. Patients could receive up to 4 courses of DLIs within 1 year after the first infusion.
   c. CAR-T-cell therapy for Ph-negative ALL is recommended. CAR-T-cell therapy for AML can enter clinical trials.

C. Second transplant

A second transplant can be chosen if the patient is fit enough to proceed with a second transplant. A different donor from the first HSCT is recommended for patients with HLA-loss relapse.

D. Treatment of extramedullary relapse (EMR)

According to the extent of the extramedullary lesion, site, occurrence time, and presence of isolated EMR, in addition to local surgery and intrathecal chemotherapy, systematic chemotherapy and/or radiotherapy plus DLI is recommended for most patients.

E. Clinical trials

Clinical trials, including investigations of novel cellular therapies such as CAR-T cells and the use of new targeted drugs, are always recommended as the first treatment option whenever possible for relapse after allo-HSCT.

5.2. Preemptive therapy or intervention

Preemptive therapy or intervention is triggered by the detection of MRD positivity. The application of modified preemptive DLIs and IFN-α in the setting of MRD positivity greatly extends the refinement of MRD-directed approaches. The use of CAR-T cells [11] and other novel targeted agents represents progress in the implementation of MRD-triggered procedures [16,35–37,59,85,86].

5.2.1. Preemptively modified DLI

Preemptive DLI based on MRD or chimaerism monitoring has been implemented worldwide to enhance the graft-versus-leukaemia (GVL) effect following allo-HSCT (Table 4) [4,21,35–37]. Recently, the benefit of early intervention with DLI in the prevention of morphologic relapse was demonstrated in high-risk t (8; 21) patients based on post-HSCT *RUNX1-RUNX1T1* transcript testing [19,24]. The cell dose and prevention of GVHD caused by the modified preemptive DLI are almost identical to those caused by the therapeutic DLI. Patients could receive repeated DLIs every 3–6 months depending on MRD and GVHD status after each infusion: repeated DLIs were given at 3 months after the first infusion with persistent positive MRD and no GVHD, while repeated DLIs were delayed to 6 months with negative MRD. Administration of DLI according to mixed chimaerism has been reported to decrease the relapse rate and favourably affect outcomes [60,62,87].

5.2.2. Novel therapies

Researchers at Peking University have suggested that donor-derived anti-CD19 CAR-T-cell therapy may be safer and more effective than chemotherapy followed by DLI for MRD-positive B-ALL patients after allo-HSCT (Table 3) [11]. Adoptive NK cell infusion is a promising immunotherapy for myeloid malignancy [88–90].

For Ph-positive ALL, preemptive TKI initiation was based on *BCR::ABL1* molecular monitoring, and the choice of TKI was based on ABL kinase mutation [45,91]. Recent findings underline the importance of preemptive TKI in comparison with prophylactic use [91]. The safety and efficacy of blinatumomab or INO with DLI in treating post-HSCT MRD-positive ALL patients have also been demonstrated [80,92]. The efficacy of HMA alone or combined with venetoclax or IFN-α in MRD-positive patients after allo-HSCT has been evaluated [64,93]. Specifically, avapritinib is effective for the treatment of MRD in patients with AML with t (8; 21) and KIT mutations who fail to respond to immunotherapy after HSCT [94].

5.2.3. IFN-α

IFN-α has been shown to be safe and effective in treating AML, MDS, and ALL patients with post-HSCT MRD, and long-term survival has improved [24–26,95]. In the t (8; 21) subgroup, AML patients with low-level and intermediate-level *RUNX1-RUNX1T1* could benefit more from preemptive IFN-α therapy than from DLI, while outcomes were comparable between preemptive IFN-α therapy and DLI in patients with high levels of RUNX1-RUNX1T1 [24]. Preemptive low-dose interleukin (IL)-2 may be an alternative method for patients who develop late-onset MRD after allo-HSCT, particularly for patients who cannot receive preemptive DLI [96].

5.2.4. Limitations of MRD-directed interventions

First, false-positive or false-negative MRD results due to the insufficient specificity and sensitivity of the monitoring methods hamper recurrence prediction. Second, the best cut-off for MRD positivity and the optimal timing of intervention remain controversial. Third, the efficiency of MRD-directed interventions has not been investigated in randomized clinical trials, and bias may be inevitable. Well-designed prospective clinical trials are warranted to confirm the results of the currently available MRD-directed interventions.

Recommendations: Preemptive therapy (Fig. 1).

Patients with molecular relapse after transplantation.

a. Timing of intervention or the suitable population: please see the criteria for positive MRD.

b. Chemotherapy combined with DLI is recommended for Ph-negative leukaemia patients. DLI can also be performed without prior chemotherapy; however, it is not recommended for patients with active GVHD. The dose with modified preemptive DLI are almost identical to those of therapeutic DLI. MRD- and GVHD-guided repeated DLIs can be performed at 3–6 months after the first infusion.
c. IFN-α is an alternative method for relapse intervention, especially for patients with low-level MRD.
d. Targeted drugs, such as TKIs for Ph-positive leukaemia and FLT3-ITD AML; other novel agents, such as venetoclax, HMA combined with chemotherapy for AML/MDS; and antibodies for B-ALL.
e. Clinical trials are recommended for B-ALL patients who are MRD-positive post-HSCT to explore new cellular therapies, such as CAR-T cells.

For patients who failed preemptive interventions and relapsed, please see the recommendations for Treatment of Morphological Relapse post-HSCT.

5.3. Prophylaxis for advanced-stage leukaemia

Several strategies for relapse prophylaxis for advanced-stage leukaemia after HSCT can be considered, including choosing the ideal donor to exert the GVL effect, optimizing the conditioning regimen, prophylactic immunomodulation, and maintenance therapy post-HSCT. Chinese researchers have integrated these attempts with sequential MRD-guided modified DLIs and developed "total therapy" to remarkably improve the prognosis of refractory/relapsed leukaemia patients, even in a haploidentical setting [22,23].

5.3.1. Donor selection

Data from China revealed better survival and a role for immune cells in the superior antileukaemia effects of haplo-HSCT compared with those of matched HSCT [5,6,39,97]. Therefore, as recommended by the CSH HSCT workshop, unmanipulated haploidentical donors, especially offspring donors, can be considered to establish an adapted algorithm for donor selection in patients at high risk of relapse [27]. In addition, several groups have recently indicated that coinfusion of unrelated cord blood units in haploidentical HSCTs can improve survival in leukaemia patients [98,99].

5.3.2. Intensifying and modulating the conditioning regimen

Recent Chinese randomized studies comparing classical regimens revealed that total body irradiation (TBI) plus cyclophosphamide (Cy) or busulfan (Bu) plus fludarabine (Flu) yielded relapse rates similar to those of Bu plus Cy among patients with leukaemia who achieved CR [100,101]. For patients with advanced leukaemia, Chinese scholars have suggested that either an intensified myeloablative conditioning (MAC) regimen (e.g., decitabine-based intensive conditioning) or the addition of novel agents to a moderate conditioning regimen (e.g., adding melphalan to BuFlu) may further enhance the antileukaemia effect without increasing toxicity [102,103]. In addition, decitabine combined with other agents, such as G-CSF, idarubicin, venetoclax, or N-acetyl-L-cysteine, has been reported to be effective in decreasing relapse and/or enhancing platelet recovery after HSCT [104–107].

5.3.3. Prophylactic modified DLI

Two large registry or prospective studies in China showed that the use of modified prophylactic DLI (pro-DLI) during the immediate post-transplantation period improved long-term survival and ensured quality of life compared to patients with refractory/relapsed leukaemia not receiving pro-DLI [22,23](Table 4). More recently, early scheduled pro-DLI rather than preemptive DLI (pre-DLI) after detectable MRD yielded reduced posttransplant relapse and improved long-term survival in high-risk patients with AL [108]. The time points at which modified prophylactic DLI was used were not defined [60,62,97,108]. In a prospective study from Peking University, modified prophylactic DLI was administered 30 days after MSD HSCT or 45–60 days after haploidentical HSCT [23]. The modified prophylactic DLI regimen is almost identical across Chinese centres, with a $CD3^+$ cell dose of approximately 3×10^7/kg and STI for 6–8 weeks after infusion.

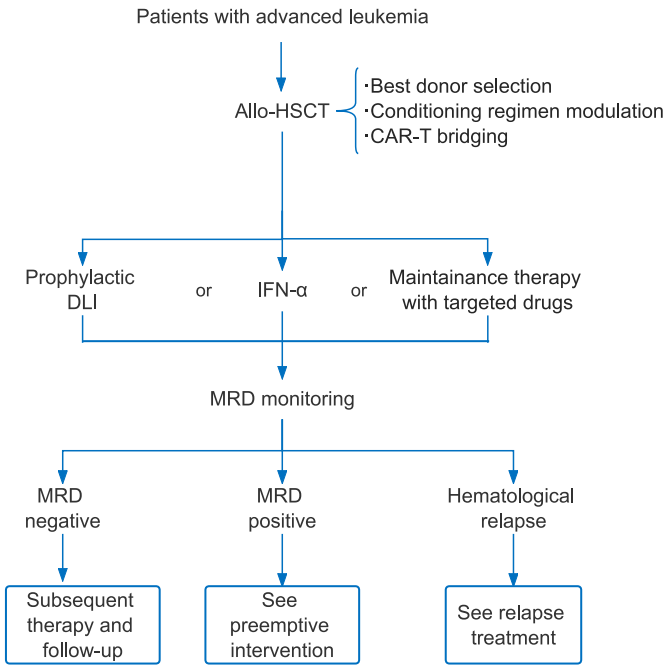

Fig. 2. Recommendation for relapse prophylaxis among advanced leukaemia patients after allogeneic stem cell transplantation. Several strategies for relapse prophylaxis for advanced-stage leukaemia after HSCT can be considered, including choosing the ideal donor to exert the GVL effect, optimizing the conditioning regimen, prophylactic immunomodulation, and maintenance therapy post-HSCT.

5.3.4. Novel cellular methods

Both CAR-T-cell bridging to HSCT for advanced ALL [1,67] and NK-cell infusion or early after haplo-HSCT for myeloid malignancy [89,90] can improve post-HSCT outcomes. Considering the perfect short-term response along with the high risk of disease recurrence, CAR-T cells may be used as a bridge to allo-HSCT or incorporated into conditioning regimens rather than as a replacement [12,109,110]. Future registry-based and prospective studies will hopefully provide the needed data to risk-stratify the recipients of CAR-T-cell therapy and the consolidation role of allo-HSCT [1,111].

5.3.5. Maintenance therapy

Imatinib prophylaxis achieved long-term outcomes similar to those of dasatinib for patients with Ph-positive ALL undergoing allo-HSCT in CR1 [112]. Hypomethylating agents used alone or in combination with other strategies, including G-CSF, venetoclax or DLI, offers promising prophylaxis in the post-HSCT maintenance setting for high-risk leukaemia patients [113–117]. Recent multicentre randomized studies revealed that FLT3 inhibitors can significantly improve survival in FLT3-positive AML patients [118–121]. Recent multi-centre study revealed the efficacy of blinatumomab as maintenance therapy for B-ALL following allo-HSCT [122]. Chidamide maintenance therapy has been reported to be feasible for high-risk patients with T-cell leukaemia [123].

5.3.6. Total therapy for refractory/relapsed leukaemia

Total therapy included allo-HSCT, planned prophylactic DLI, MRD and GVHD-guided multiple pDLI (pro- and pre-DLI), and MRD

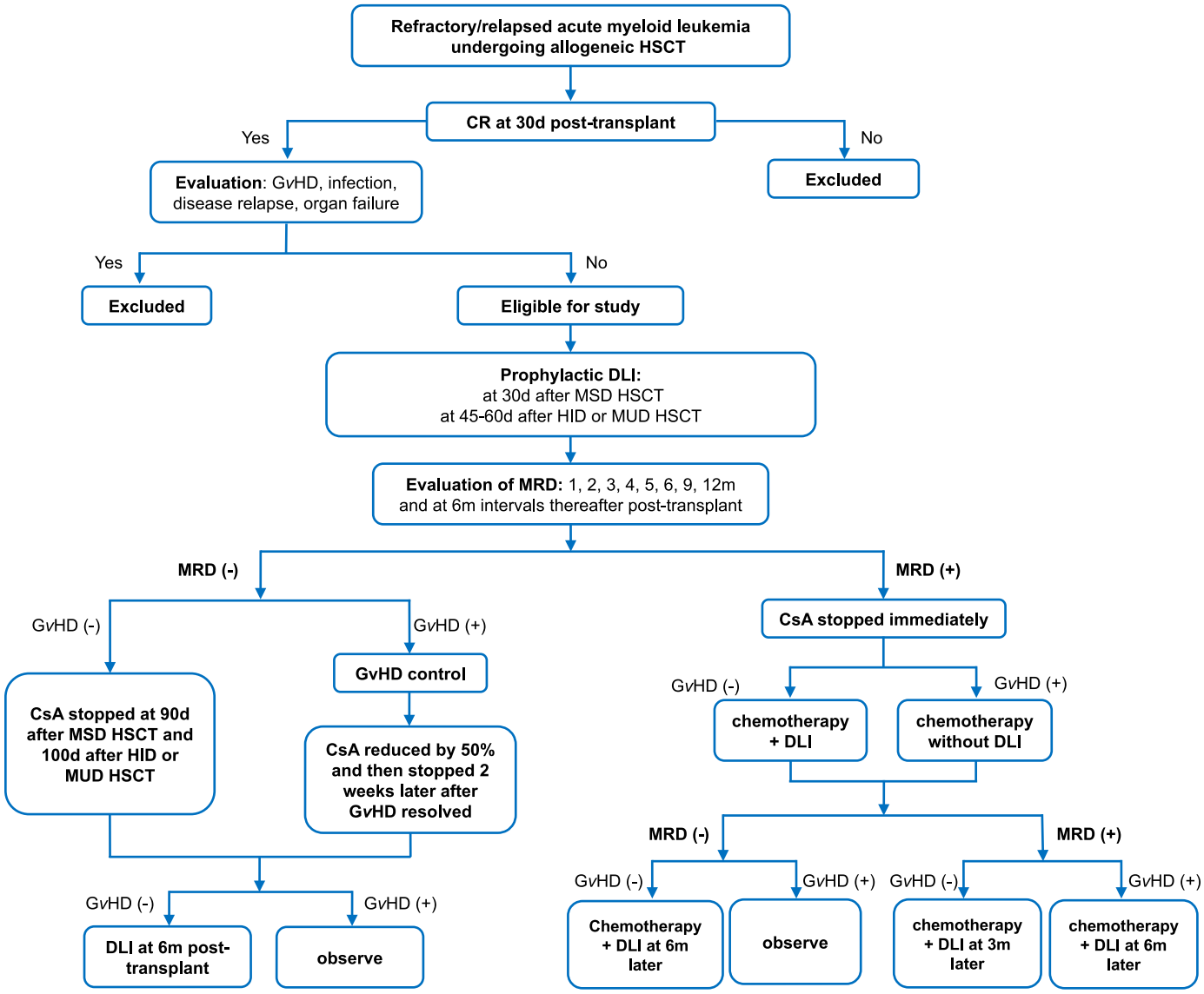

Fig. 3. "Total therapy" algorithm for relapsed/refractory leukaemia patients. Total therapy included allo-HSCT, planned prophylactic DLI, MRD and GVHD-guided multiple pDLI (pro- and pre-DLI), and MRD monitoring.

monitoring. If the patients achieved CR at 30 days after HSCT and had no evidence of severe infection, organ failure, or active GVHD at the time of planned DLI, prophylactic DLI was administered at 30–60 days after HSCT. Subsequently, multiple DLIs were administered based on the MRD results and whether the patients developed GVHD. Total therapy is associated not only with greater long-term survival but also with satisfactory quality of life for refractory or relapsed leukaemia patients compared with those receiving standard of care therapy reported previously. Therefore, the establishment of "total therapy" represents a great step forward for patients who have undergone transplantation for refractory/relapsed leukaemia [21–23].

Recommendations: prophylaxis for advanced leukaemia (Fig. 2).

A. Donor selection: Haploidentical donors should be considered in the absence of a matched donor or preferred to a matched donor in experienced centres, especially for leukaemia patients with positive pre-HSCT MRD.
B. Modulation of the conditioning regimen: novel agents that have superior antitumour activity and/or less toxicity, either alone or in combination, could be added to conditioning regimens.
C. Immunomodulation
   a. Prophylactic DLI after HSCT can be chosen for patients without active GVHD, especially for patients without targeted drugs. Subsequent MRD tests and GVHD-guided multiple DLIs are suggested. The timing of modified prophylactic DLI can be decided according to the donor source and centre experience (see above).
   b. Cytokines and novel cellular immunotherapy: cytokines, such as IFN-α and IL-2, can be utilized. NK cell infusions and CAR-T cells have entered clinical trials.
D. For targeted drugs, prophylactic use of TKIs for Ph-positive ALL or FLT3 inhibitors for FLT3-positive AML patients is considered for myeloid and platelet recovery.
E. For patients with refractory or relapsed disease pre-HSCT, relapse prophylaxis with a "total therapy" strategy (Fig. 3) should be implemented.
F. Patients with refractory or relapsed disease could be recommended for clinical trials to explore new methods, such as novel conditioning regimens and new maintenance agents, for relapse prophylaxis.

For patients who relapsed or converted to MRD-positive after prophylaxis, please see the sections on relapse treatment or preemptive

intervention after allo-HSCT.

6. Summary and perspective

In conclusion, a consensus has been reached regarding post-HSCT relapse management, especially in China. The establishment of a "total therapy" strategy with risk-directed DLI and IFN-α as the foundation represents a great step forward pioneered by Chinese scholars. Randomized controlled trials are scarce for most conditions since decisions involving transplantation are complex, and the basis of the biological and immunological mechanisms involved needs to be elucidated. We expect that targeted molecular agents and cellular therapy combined with MRD monitoring will complement HSCT to further improve post-HSCT outcomes. In summary, we hope that the consensus periodically updated by Chinese scholars will cover the latest cutting-edge developments and inspire progress in post-HSCT relapse management.

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Authors' contributions

WY and HXJ assembled the sections and wrote the final version of the manuscript. WY, CYJ, CJ, HMZ, HJD, HJ, HH, LYR, LDH, LQF, LY, JEL, JM,SYP, TXW, WDP, XLH, XKL, ZX, ZXH, and HXJ reviewed the literature, wrote first drafts of specific sections, read and approved the final manuscript.

CRediT authorship contribution statement

Yu Wang: Conceptualization. **Ying-Jun Chang:** Conceptualization. **Jing Chen:** Data curation. **Mingzhe Han:** Data curation. **JianDa Hu:** Data curation. **Jiong Hu:** Formal analysis. **He Huang:** Formal analysis. **Yongrong Lai:** Formal analysis. **Daihong Liu:** Investigation. **Qifa Liu:** Investigation. **Yi Luo:** Investigation. **Er-lie Jiang:** Methodology. **Ming Jiang:** Methodology. **Yongping Song:** Methodology. **Xiao-Wen Tang:** Project administration. **Depei Wu:** Project administration. **Ling-Hui Xia:** Resources. **Kailin Xu:** Resources. **Xi Zhang:** Software. **Xiao-Hui Zhang:** Supervision. **Xiaojun Huang:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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