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The consensus on the monitoring, treatment, and prevention of leukemia relapse after allogeneic hematopoietic stem cell transplantation in China

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important curative therapy for patients with leukemia. However, relapse remains the leading cause of death after transplantation. In recent years, substantial progress has been made by Chinese physicians in the field of establishment of novel transplant modality, patient selection, minimal residual disease (MRD) monitoring, and immunological therapies, such as modified donor lymphocyte infusion (DLI) and chimeric antigen receptor T (CART) cells, as well as MRD-directed intervention for relapse. Most of these unique systems are distinct from those in the Western world. In this consensus, we reviewed the efficacy of post-HSCT relapse management practice from available Chinese studies on behalf of the HSCT workgroup of the Chinese Society of Hematology, Chinese Medical Association, and compared these studies with the consensus or guidelines outside China. We summarized the consensus on routine practices of post-HSCT relapse management in China and focused on the recommendations of MRD monitoring, risk stratification directed strategies, and modified DLI system. This consensus will likely contribute to the standardization of post-HSCT relapse management in China and become an inspiration for further international cooperation to refine global practices.

KEY WORDS: minimal residual disease, donor lymphocyte infusion, targeted therapy, acute leukemia, myelodysplastic syndrome

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) continues to be the major curative option for patients with leukemia [1-5].Leukemia relapse, however, remains the leading cause of death after transplantation [6, 7]. The data from the International Bone Marrow Transplantation Registry (CIBMTR) showed that relapse was responsible for 46% and 57% of all deaths beyond 100d post-HSCT in unrelated and identical sibling transplantation, respectively [8].According to the data from Peking University Institute of Hematology, the cumulative incidence of relapse-related mortality at 10 years among patients after haploidentical and HLA-identical sibling transplantation was 15.6% and 16.7%, which accounted for 32% and 42% of deaths, respectively [7].Once relapse occurs, the prognosis is poor. Although different opinions still exist and there is no standard approach to post-HSCT relapse management, it must be acknowledged that significant improvements have been achieved in the prevention and treatment of post-HSCT relapse in recent years [4, 9-15].

The present guidelines focus on monitoring, prevention, and treatment for post-HSCT relapse. Three major initiatives were proposed: (1) to refine, implement, and study proposed definitions for post-HSCT relapse and for monitoring of minimal residual disease, or more appropriately, measurable residual disease (MRD)[16-25]; (2) to define the role of currently available or new treatment options, including both nonimmunologic therapies, such as preparative regimens and post-transplant drug therapy, and immunologic interventions, such as modified donor lymphocyte infusion (DLI)[13, 26]and chimeric antigen receptor (CAR) T cells[27]; and (3) to make recommendations for an individualized, risk-adapted strategy for the early identification and prevention of relapse in the post-HSCT period[4, 13, 18, 27-35]. This consensus will likely contribute to the standardization of post-HSCT relapse managements in China and become an inspiration for further international cooperation to refine global practices.

Methods

Composition of the panel

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

Scope of the review

Computerized literature searches of the PubMed, and Medline databases in the English language were conducted using key words relevant to the monitoring, prevention, and treatment of leukemia relapse after allo-HSCT. The HSCT workgroup of CSH updated the recommendations from a consensus conference based on differences in the post-HSCT relapse practices in China and the Western world [14, 15]. The vast majority of recommendations were category 2A recommendations [36],

that is, they are based on low-level evidence and there is uniform panel consensus.

1. Definition and Classification of leukemia 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 hematologic relapse, cytogenetic, and/or molecular recurrence, according to the tumor burden[3, 37].The relapse can also be categorized as intramedullary relapse, extramedullary relapse, or both[37].

i). Hematologic relapse is defined as the reappearance of leukemia cells in peripheral blood or blast cells accounting for at least 5% in the bone marrow, or extramedullary infiltration for patients who achieve complete remission after HSCT [38];

ii). Cytogenetic relapse is defined as the reappearance of the initial cytogenetic abnormalities or the conversion from complete donor chimerism to mixed donor chimerism of sex chromosomes (there is no uniform standard, and this does not always parallel the increase in leukemia cells), yet has not reached hematologic relapse;

iii). Molecular relapse is defined as the reoccurrence of MRD as assessed by multiparameter flow cytometry (MFC) and/or polymerase chain reaction (PCR), if studied pretreatment [38]. *See criteria for MRD* below.

In addition, leukemia relapse is also classified as donor- or recipient-derived relapse, according to the source of tumor cells.

2. Leukemia relapse monitoring

Integrated methods, including morphological, cytogenetic, immunological, and molecular techniques, have been applied to monitor leukemia relapse [3, 39]. In recent years, more attention has been paid to the MRD, which could be used not only to predict hematological relapse, but also for stratification-directed intervention to decrease hematological relapse [4, 39-42].The term MRD is used to describe low-level disease, which is not detectable by conventional cytomorphology and denotes the presence of leukemia cells down to levels of $1:10^4$ to $1:10^6$ white blood cells, compared with 1:20 in morphology-based assessments [43]. Approaches for MRD determination are based either on the discrimination of leukemia cells from normal physiological counterparts or the identification of specific genetic aberrations, and/or specific immunoglobulin (IG) or T-cell receptor (TCR) gene rearrangements by MFC, real-time PCR (RT-PCR), and/or next-generation sequencing (NGS) (*Table 1*)[40-42].

Several international groups, such as the National Cancer institute (NCI) and the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT) [15], have summarized the MRD monitoring after HSCT or recommended guidelines for specific diseases. The current data provide further valuable information for post-HSCT MRD monitoring as guidance for MRD-directed interventions, especially among patients with some subtypes of leukemia, which potentiated the evidence from the Western world [14, 15].In the current consensus,

we will discuss the techniques used in China for MRD assessment, the cutoff values of different biomarkers, and the prognostic significance of MRD in allo-HSCT settings [4, 13, 16-19, 24, 44-46].

2.1 MRD monitoring methods

MRD has been identified as an accepted prognostic indicator for patients with either acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). Here, we focused on MFC and RT-PCR[4, 13, 16-19, 24, 44-47], because i) the sensitivity for clarification of the chromosomal abnormalities by the classical chromosomal banding analysis and/or fluorescence in situ hybridization (FISH) is limited, and; ii) NGS and digital PCR have not been routinely used in clinics in China.

2.1.1 MRD by MFC

Leukemia-associated aberrant immunophenotypes (LAIPs) could be identified by MFC in more than 90% of cases of AL, with a sensitivity of 10^{-3} to 10^{-4}[22, 24, 43].With the rapid development of haploidentical HSCT, the effect of positive MRD on haploidentical transplant outcomes deserves attention. Zhao et al. reported that, among 139 patients with ALL (105 receiving haploidentical transplant), LAIP-positive patients had a lower leukemia-free survival (LFS) (54% vs. 80%) and a higher cumulative incidence of relapse (CIR) (54% vs. 8%) after allo-HSCT than did LAIP-negative patients [24]. Moreover, LAIP-positive status after the second month post-HSCT was a predictor of CIR. In the booming haplo-HSCT era, comparative study evaluating the different prognostic value of MRD monitoring after haploidentical HSCT or matched donor transplant is lacking. A recent study, for the first time, showed that, in contrast to matched sibling donor (MSD) HSCT, there were no negative effects of pre-transplant MRD on relapse in the unmanipulated haplo-SCT modality, suggesting that unmanipulated haplo-SCT may be better than MSD HSCT in eradicating pre-MRD [16, 48].

Although there are no standardized protocols or consensus for panel design, a cutoff of 0.1% was included and found relevant in most published studies to date. Therefore, the European LeukemiaNet MRD Working Party recommends using 0.1% as the threshold to distinguish MRD-positive from MRD-negative patients with AML [49]. A cutoff of 0.01% can be achieved in B-ALL and T-ALL, which was accepted by most researchers [22, 47]. Currently, MFC monitoring has the advantages of relatively low expense and results that are obtained rapidly compared with other highly sensitive molecular methods, although precise MRD cutoff levels and detection time-point for patients with acute leukemia (AL) should be investigated further. Also, one must always keep in mind that there are high rates of false-positive and -negative MRD-tests in AML and reasons to that have recently been reviewed by Hourigan CS et al. [50].

2.1.2 MRD by RT-PCR

PCR assays for MRD monitoring are based on the detection of leukemic-specific

targets, such as a fusion gene, mutated or overexpressed gene, as well as the pan-leukemic marker Wilms' tumor (WT1) gene, with the sensitivity ranging from 10^{-5} to 10^{-6}[6, 19, 30, 43, 47, 51]. If the genetic abnormalities were detected at the initial diagnosis of the leukemia, then RT-PCR is an important tool to monitor the existence of the abnormality.

LEUKEMIA-SPECIFIC MOLECULAR TARGETS

Core-binding factor (CBF)

Previous studies from China revealed that patients with t(8;21) or inv(16) AML, who are considered high-risk one by MRD-directed risk stratification, could benefit from allo-HSCT[4, 46, 52]. Subsequent study showed that *RUNX1/RUNX1T1*-based MRD monitoring early after transplant enables rapid identification of t(8;21) AML patients with high risk of relapse if these cases did not achieve >3-log reduction in *RUNX1-RUNX1T1* transcripts when compared with the pretreatment baseline level [19]. Qin et al. further confirmed the results [18]. With regard to inv(16) AML, Tang et al. observed that all seven out of 53 cases who either did not achieve major molecular remission (MMR, defined as <3-log reduction in *CBFβ-MYH11* transcripts) within the first 3 months (n = 4) or lost MMR later (n = 3) relapsed after allo-HSCT [30].

Lysine (K)-specific methyltransferase 2A (KMT2A, also termed MLL)-rearrangement

Wang et al. previously reported an improved outcome in the poor prognostic subgroup of patients with MLL–rearranged AL who underwent allo-HSCT [53]. Liu et al. first showed that the 3-year CIR in KMT2A-positive patients was significantly higher than that in KMT2A-negative patients (93% vs. 12%, P < 0.001) after allo-HSCT [54].

Philadelphia chromosome-positive (Ph–positive) leukemia

The clinical value of monitoring *BCR-ABL1* in chronic myeloid leukemia (CML) patients after allo-HSCT has been well demonstrated [55]. In Ph–positive ALL, Chen et al. documented that *BCR-ABL1* monitoring by qRT-PCR can guide maintenance therapy with imatinib after allo-HSCT [56].

Nucleophosmin 1 (NPM1) gene and FLT3 gene mutation

A recent study showed that the persistence or increase of >10% of nucleophosmin gene (NPM1mut)/ABL1 copies predicts for relapse after allo-HSCT [57]. Some scholars demonstrated the complexity of using molecular techniques to monitor MRD due to Fms-like Tyrosine Kinase 3 Internal Tandem Duplication (*FLT3*-ITD) AML changes in the mutation patterns at relapse [51].

Other leukemia-specific genes

The association of other fusion genes (with transcript levels more than 0), such as translocation liposarcoma-ETS-related gene *(TLS-ERG), E2A-PBX1, SIL-TAL1,* and *ETV6-RUNX1* (also known as *TEL-AML1*), with relapse after allo-HSCT were first reported by researchers from Peking University [17, 20, 44, 58].

PAN-LEUKEMIA MOLECULAR TARGETS

Zhao et al. analyzed the results of a quantitative evaluation of WT1 expression in a

large-scale study (*n* = 138), and found that WT1 expression ≥0.60% was associated with a worse LFS (HR = 4.8; *P*< 0.001) and a worse overall survival (OS) (HR = 2.8; *P* = 0.007) [23]. In addition, more than 60% of patients with WT1 expressions >1.0% eventually underwent hematological relapse. Zhang et al. observed that increased WT1 gene expression levels at +60 and +90 days was associated with higher CIR (*P*< 0.001, *P* = 0.003), lower disease free survival (DFS) (*P* = 0.004, *P* = 0.006), and lower OS (*P* = 0.004, *P* = 0.007) in patients with T-ALL after allo-HSCT [59].

Each of the abovementioned MRD monitoring methods has its own advantages and disadvantages [39, 43, 47]. Thus, multiple parameters for MRD monitoring are needed to guide suitable interventions without overtreatment, ultimately leading to a further reduction in the risk of transplant-related mortality (TRM). Moreover, after comparing the sensitivity and specificity of diverse, multiple cut-off values based on WT1 and MFC assays, Zhao et al. reported that combinative MRD (named MRDco+) positivity could be used to predict leukemia relapse with higher sensitivity and without compromising specificity [45]. In addition, NGS and digital PCR for MRD detection for gene mutation represent promising tools, although currently these techniques are time-consuming and costly [60, 61].

2.2 Recommendations: criteria (indications for intervention therapy) and timing for MRD detection

As mentioned above, serial MRD monitoring with more than one modality is critically important.

2.2.1 Criteria for determining MRD positivity

2.2.1.1 Acute leukemia or myelodysplastic syndrome (MDS) without specific fusion gene markers:

WT1 and/or LAIP are often used as biological markers for MRD surveillance without standard cut-off values. The following criteria are adopted at the Peking University Institute of Hematology. At least one of the following criteria should be met between 2 months and 1 year after HSCT:

a. Two consecutive positive WT1 with the interval of 10 ~ 14d; the cut-off value was defined as 0.6% for adults and 1.5% for children;
b. Two consecutive positive MFC tests with the interval of 10-14d;
c. Simultaneous WT1 and MFC positivity in one sample.

2.2.1.2 Leukemia with specific fusion gene

Philadelphia Chromosome–Positive ALL (Ph$^+$ ALL)

a. without *BCR-ABL1* transcripts converting to negative after HSCT (negative defined as qPCR detection of *BCR-ABL1* expression of 0 with the sensitivity of less than 5 copies);
b. with no decreasing trend in two consecutive tests (with the interval of at least 1 month);
c. higher than 1% at any time point after HSCT, or conversion from negative to positive.

Chronic myeloid leukemia (CML)

a. The decrease of *BCR-ABL1* transcripts is less than 2 log from the baseline at 1 month after HSCT and shows no decreasing trend in two consecutive tests (with an interval of less than 2 months);
b. not reaching the criteria of major molecular remission (MMR, defined as the decrease of *BCR-ABL1* transcripts more than 3 log from the baseline);
c. *BCR-ABL1* conversion from negative to positive or increasing by 1 log in two consecutive tests (within the interval of 2 months).

Leukemia with RUNX1-RUNX1IT1

The decrease of *RUNX1-RUNX1IT1* is less than 3 log compared with the baseline, or higher than 0.4% after HSCT.

Leukemia with CBFβ-MYH11

The decrease of *CBFβ-MYH11* is less than 3 log compared with the baseline.

Other less frequent fusion genes

The levels of the genes, including *MLL, TLS-ERG, E2A-PBX1, SIL-TAL1,* and *ETV6-RUNX1,* detected more than 0 are considered MRD-positive.

2.2.2 Monitoring frequency and sample source

2.2.2.1 Frequency

a. It is recommended to regularly detect bone marrow morphology, MRD, and chimeric status at +1, +2, +3, +4, +6, +9, +12, +18, +24, +36, +48, and +60 months after transplantation. Each center can follow its own schedules according to the actual situation, and increase the frequency of testing when necessary;
b. Patients with detectable MRD are suggested for re-check within two weeks.

2.2.2.2 Sample source

a. Once relapse occurs, the bone marrow morphology, immunophenotype, cytogenetics, molecular markers, and chimerism should be tested;
b. The detection of chimerism can be done using bone marrow and/or peripheral blood sample, with bone marrow testing shown as more sensitive in some studies;
c. Bone marrow samples should be preferred for other MRD tests.

3 Treatment, and prevention of leukemia relapse

Strategies for relapse after allo-HSCT include the treatment for hematologic relapse, preemptive intervention therapy for patients with positive MRD, and relapse prophylaxis for refractory/relapsed patients [4, 11-13, 27, 31-33, 62]. Currently available or new treatment options include both nonimmunologic therapies, such as chemotherapy and radiation, and immunologic interventions, such as immune suppression (IS) withdrawal, DLI [4, 12, 31-33, 63-65], CART cell-based approaches [27, 66], and second transplant [67, 68]. To date, the simplest and most well-studied immune interventions are the withdrawal of IS and DLI [4, 12, 31-33, 63-65]. The novel targeted drugs and cellular therapies have achieved promising outcomes, and thus should be encouraged to be incorporated into clinical trials. On the other hand, we should always be mindful that any new cellular therapy ultimately must be judged in comparison with classical DLI or second HSCT[67, 68].Finally, management of

post-HSCT relapse may require the combined use of immunologic approaches with novel chemotherapy or biologic therapies in a multimodality approach [4, 11-13, 27, 31-33, 62].

DLI has been a powerful weapon in the treatment of relapsed or persistent hematological malignancies after allo-HSCT since it was first successfully used by Kolb et al. in 1990 to treat CML relapse [69]. In the past fifteen years, researchers from Peking University focused on enhancing the GVL or graft-versus-tumor effects of the infused donor T cells, while decreasing DLI-related toxicities, such as graft-versus-host disease (GVHD) and aplasia. Based on the immunological regulatory effects of granulocyte colony-stimulating factor (G-CSF), such as the ability to polarize T cells from the Th1 to Th2 phenotype and to induce T cell hyporesponsiveness[70, 71], a modified DLI protocol was pioneered by Huang et al. in 2003 [72]. This protocol entails the infusion of G-CSF-mobilized peripheral blood progenitor cells, followed by the use of short-term immunosuppressive (STI) agents for GVHD prophylaxis. Further investigation showed that using immunosuppressive agents for 2-to-4 weeks may reduce DLI-associated acute GVHD without influencing relapse and survival after modified DLI [11, 73].

3.1 Treatment of Hematologic Relapse

Currently, donor cell therapy remains the foundation of most approaches to induce remission for leukemia patients who relapsed post-HSCT [11, 13, 31, 64], although there is no standard approach for hematologic relapse. In addition, target drugs, such as tyrosine kinase inhibitors (TKIs), have been successfully used for relapse treatment.

Withdrawal of immune suppression

Once the diagnosis of hematologic relapse is made, withdrawal of immunosuppression (WIS) is routinely considered [74]. However, WIS is very unlikely (<5%) to result in clinically significant benefit, at least in morphologic relapse [55]. Responses to WIS are most likely to occur in patients relapsing with a low blast percentage, or with cytogenetic or molecular recurrence. Concurrent presence of GVHD at relapse is a major complicating variable, in which a patient who was not ‘‘protected’’ against relapse by GVHD in the first place is unlikely to benefit from any further GVHD. Thus, WIS is considered for patients who relapsed without onset of GVHD [75].

Modified DLI for post-HSCT relapse treatment

Modified DLI, a novel transplant technique system contributed by Chinese scholars to the global practice of allo-HSCT [4, 11, 13, 31, 33], has been widely used for relapse therapy [64]. In 2007, Huang’s group for the first time reported the efficacy and safety of modified DLI in treating 20 patients who relapsed after haploidentical allografts [31]. They showed that eight cases survived in complete remission (CR) for a median follow-up of 1118 days. The two-year LFS was 40%. Acute GVHD grade II–IV occurred in six patients after DLI. These data show the modified DLI protocol to be a potentially effective therapeutic option for patients who relapse after haploidentical HSCT, which markedly broaden the applicability of DLI in various transplant

modalities [11, 12, 63].

Adjunctive strategies to improve DLI, including cytoreduction before DLI, combination of novel targeted agents with DLI, and novel approaches to enhance T cell function or specificity are explored [11, 12, 63].Huang's group also demonstrated that, compared with chemotherapy alone, treating relapsed acute leukemia patients with chemotherapy followed by modified DLI could achieve a higher CR rate, longer CR duration, lower CIR, and improved DFS[12]. Tang et al.[76]reported on 16 patients with relapsed AL treated with IFNα plus G-DLI. They found that IFN-a/DLI resulted in a higher CR rate (75% vs. 14%, *P*=0.001) and improved LFS (50% vs. 7%, *P*=0.05) compared with 14similar patients treated with DLI alone, albeit with increased acute GVHD (56% vs. 27%, *P*= 0.05). Overall, the modified DLI, alone or in combination with other methods, was used to treat AML relapse, ALL relapse, and MDS relapse, which had been confirmed by the studies from other centers from China and the Western world[4, 11-13, 31-33, 63, 64, 77].

Novel Cellular Therapies

In recent years, CAR T cells have been an attractive approach for any tumor with a defined target because they can activate and kill tumors in an antigen-dependent, but HLA-independent, manner *in vivo* [78]. For example, CD19-CARs have induced rapid and sustained antitumor activity in chemotherapy-refractory chronic lymphocytic leukemia, refractory/relapse B-ALL, and B cell lymphomas. These cells can also induce remission for refractory ALL and for relapse of ALL after umbilical cord blood transplantation [27, 66, 79]. Researchers from Peking University reported six ALL patients with no response to modified DLI who received one and two infusions of CAR T cells from haplo-HSCT donors [27]. Five (83.33%) achieved MRD-negative remission; one patient was discharged automatically without evaluation after developing severe thrombotic microangiopathies. Therefore, donor-derived CAR T-cell infusion seems to be an alternative effective and safe method for relapsed B-ALL after haplo-HSCT, although larger clinical studies are needed.

Targeted drug therapy

Targeted drug therapies, such as TKIs and the monoclonal antibodies (MoAb), have been exploited in previous studies [56, 80,81]. Various novel agents (non-TKIs) have demonstrated clinical activity, such as isocitrate dehydrogenase (IDH) inhibitors, with salvage regimens at relapse [81,82].

Second allo-HSCT

According to relapse interval and whether MRDs convert to negative, second transplant can be chosen if the patient has good physical status and has the willingness to proceed with a second transplant [83-85]. There is no large sample study on the outcomes of relapsed patients who received second transplants in China. According to the studies published by researchers from Europe and the U.S., second transplant with a different donor and/or conditioning intensity from the first HSCT did not entail survival benefit [67, 86].The duration of first CR, age, physical condition, disease status, and donor intention can be helpful in determining the choice of donor and conditioning regimen [67, 80, 85].

Treatment of extramedullary relapse

There is no standard treatment. According to the extramedullary lesion scope, patients can choose local treatment, systemic chemotherapy, or combined therapy [37, 87]. Local treatment includes surgical resection, intrathecal injection, and local radiotherapy. Systemic treatment includes chemotherapy, DLI, and secondary transplant [37]. Most studies have shown that local treatment alone is often accompanied by an intramedullary relapse. Therefore, systemic treatment +/-DLI to prevent intramedullary relapse is recommended by most researchers. Some ALL patients with early central nervous system relapse can choose intrathecal injection of chemotherapy drugs or whole brain plus total spinal cord radiotherapy following reduction or withdrawal of immunosuppression [14, 80].

Recommendations:

For leukemia patients who relapsed after allogeneic HSCT, the combined use of available treatment options is recommended (***Figure 1***).

Methods according to subtypes of leukemia

A. For cases with Ph-positive leukemia

The response of BCR-ABL to TKIs and the mutation of ABL kinase are considered to determine the choice of TKI and chemotherapy. Subsequent DLI is advocated after CR is achieved if there is no GVHD. The duration of TKI application is based on the results of *BCR-ABL1* monitoring. TKI is suggested to be administered for at least 1 year if the continuous monitoring of *BCR-ABL1* is negative during treatment. If *BCR-ABL1* is persistently positive or converts from negative to positive during therapy, ABL kinase mutation should be tested to decide whether to change TKI.

B. For cases with AML, Ph-negative ALL, MDS, or Ph^+ leukemia with T315I mutation

a. Before starting treatment, chimerism status should be evaluated;

b. Chemotherapy followed by DLI is preferred.

C. Central nervous system (CNS) leukemia prophylaxis for cases with ALL

All patients with ALL, independent of their chromosome abnormality, require CNS prophylaxis after CR is achieved. A common approach for patients with medullary relapsed ALL, without any evidence of prior CNS disease, is to administer intrathecal MTX as prophylaxis for a total of five times.

Second transplant*:* According to time to relapse after first HSCT and MRD status after initial treatment for relapse, second transplant can be chosen if the patient is fit enough to proceed with a second transplant.

Treatment of extramedullary relapse: According to the sites of the extramedullary lesion and concurrent medullary relapse, apart from local surgery and intrathecal chemotherapy, systematic chemotherapy and/or radiotherapy plus DLI is recommended for most cases.

Clinical trials: It is always advisable to encourage clinical trials as the first-choice whenever possible for relapse post allo-HSCT including investigation of novel cellular therapies such as CART, utilization of new targeted drugs, optimization of DLI, and so on.

3.2Preemptive therapy or intervention

Preemptive treatment strategies that initiate therapy upon detection of MRD are being investigated. Withdrawal of IS (*see the section of Hematologic Relapse Treatment*), DLI with or without prior chemotherapy, cytokines, and targeted therapies are utilized as MRD-directed preemptive interventions[4, 9, 10, 26, 63, 88-91].The application of preemptive DLI is beneficial for additional specific subgroups of patients. The implication of IFNα in the milieu of MRD, both exploited by Chinese researchers, greatly extends the implementation of MRD-directed procedures.

Modified DLI for preemptive intervention

Preemptive DLI based on MRD or chimerism monitoring has been introduced by several groups to decrease relapse rates following allo-HSCT *(Table 2)*[4, 9, 10, 26, 63, 88-91].Yan et al. prospectively studied the impact of risk stratification-directed interventions for MRD on relapse and DFS in 814 subjects with standard-risk AL who received allo-HSCT in first or second CR. Patients with high-relapse rate in a total of 709 subjects were MRD− after transplantation (Group A); 105 subjects were MRD+, 49 received low-dose interleukin (IL-2) (Group B), and 56 received modified DLI, with or without low-dose IL-2 (Group C) [4]. Post-transplantation immune suppression for GVHD was also modified based on MRD state. Group C showed significantly lower cumulative risk of relapse and higher DFS and OS than did Group B (P=0.001 and P=0.002, respectively), but did not differ from Group A. Multivariate analyses showed that MRD state and modified DLI were significantly correlated with relapse and DFS. These data provide evidence and suggest that risk stratification-directed modified DLI may reduce relapse and improve survival of subjects with standard risk acute leukemia after HSCT.

More recently, Huang's group used MRD and GVHD-guided multiple consolidation chemotherapy and DLI to prevent second relapse after DLI [13]. The 1-year CIR (22 % vs. 56 %; P< 0.0001), LFS (71 % vs. 35 %; P< 0.0001), and survival (78 % vs. 44 %; P< 0.0001) were significantly better in study cohorts than in historical controls who did not receive consolidation chemotherapy and DLIs after induction chemotherapy and DLI. In addition, the benefit of early intervention with DLI in the prevention of morphologic relapse was also presented in high-risk t(8;21) patients, based on post-HSCT *RUNX1-RUNX1T1*transcriptassessments[18, 19].DLI administration according to mixed chimerism decreased the relapse rate and favorably affected outcomes [89, 90, 92]. Therefore, preemptive DLI has been advocated by the EBMT working party [15] and the French Society of Marrow Transplantation - Cell Therapy (SFGM-TC)[88].

Targeted drugs

For example, TKI is preferred for Ph^+ leukemia. The choice of TKI should consider the

previous efficacy of drugs and ABL kinase mutation test results [55, 56]. It has been reported that TKI combined with DLI may achieve better efficacy. The efficacy of hypomethylating agents (HMA) in MRD-positive patients after allo-HSCT has been evaluated [93].

Cytokines for preemptive intervention

IFNα has been shown to augment the efficacy of donor immune cells [10].In a prospective study, Mo et al. first investigated the safety and efficacy of IFN-α use in patients with post-HSCT MRD (*n*=22).The outcomes were comparable with those of preemptive DLI (*n*=45). Later on, a larger prospective study (*n*=107) confirmed the effectiveness of MRD-directed IFNα treatment [10].Moreover, MRD-directed IFN-α treatment is also effective for patients with t(8;21) AML after allo-HSCT (Mo et al., Oncologist, accepted).

Limitations of MRD-directed interventions

Studies in the potential impact of specific interventional strategies based on MRD surveillance have not yet been fully elucidated, and several factors present challenges to studying the effectiveness of DLI in this setting. First, the efficiency of MRD-directed interventions has not been investigated in randomized clinical trials (RCTs). Second, since none of the techniques for MRD monitoring has a specificity of 100%, false-positive results may be inevitable.

Recommendations (Figure 2):

For cases with cytogenetic/molecular relapse after transplantation

a. Timing of intervention or the suitable population: please see the section of criteria for positive MRD;
b. Reduction of immunosuppressive agents: whether immunosuppressive agents were reduced depending on the onset time of MRD and GVHD status. One should be cautious within +100d post-HSCT;
c. Chemotherapy combined with DLI is recommended for Ph-negative leukemia.DLI can also be performed without prior chemotherapy, but is not recommended for patients with active GVHD;
d. IFN-α is an alternative method for relapse intervention;
e. Targeted drugs, such as TKI for Ph^+ leukemia and HMA for AML/MDS;
f. Patients with cytogenetic/molecular relapse after transplantation could be recommended for clinical trials to investigate new methods, such as CART, for preemptive intervention.
g. Well-designed prospective clinical trials are needed to confirm the outcomes of the currently available MRD-directed intervention protocols.

For patients who did not respond to preemptive treatment and relapsed, please see the recommendations for relapse treatment after allo-HSCT.

3.3 Prophylaxis for relapse

There have been several attempts to prevent relapse after allo-HSCT for advanced stage leukemia, including modification of the conditioning regimen, prophylactic immunomodulation, maintenance therapy post transplantation, and donor selection

tactics[94-99].Chinese scholars integrated these maneuvers with sequential MRD-guided interventions and the prognosis of refractory/relapsed leukemia was thereby remarkably improved, even in the haploidentical HSCT setting. In addition, choosing haploidentical donors in some specified situations has exerted superior GVL effect compared with matched donor HSCT.

Donor selection

Published data from China confirmed that haploidentical transplantation achieved a lower relapse rate and improved survival as compared with identical sibling transplantation for patients with high relapse risk [16, 100, 101].These data suggest that, in the absence of a matched donor, haploidentical donor HSCT can yield a satisfactory outcome and have a stronger GVL effect in some situations. Therefore, as discussed by Ruggeri on behalf of the EBMT working party, unmanipulated haploidentical donor transplant must be considered to establish the adapted algorithm for donor selection in this setting of patients in urgent need of transplant [94].

Intensifying and modulation of conditioning regimen

In comparison with myeloablative conditioning (MAC), reduced-intensity conditioning (RIC) yielded higher relapse rate after MSD, unrelated donor (URD), or haploidentical HSCT for high-risk AML patients in EBMT studies [94, 102, 103]. Based on the superior anti-leukemia effect of MAC compared with RIC, some authors suggested that either an idarubicin-intensified regimen or sequential use of clofarabine or thiotepa and RIC may further enhance the anti-leukemia effect of the conditioning regimens for high-risk patients without increasing toxicity[95-99].Previous studies have shown that conditioning regimens containing G-CSF can reduce the relapse rate and improve the survival of refractory/relapsed AML patients after transplantation [104].

Early reduction of immunosuppression

It is suggested that the reduction of immunosuppressive agents should be applied with caution within 100 days after haploidentical transplantation and within 60 days of unrelated umbilical cord blood transplantation or HLA-matched sibling transplantation.

Prophylactic modified DLI

The role of prophylactic DLI has been tested in patients with high-risk leukemia *(Table 3)* [11, 29, 32, 33, 105-111].Two previous retrospective studies in China showed that the use of prophylactic DLI (pDLI) reduced the CIR from 66% to 46% and from 55% to 36% after MSD and haploidentical HSCT, as compared with similar patients with refractory/relapsed leukemia not receiving pDLI. Three-year LFS increased from 9% to 29% and from 11% to 22%, respectively [29, 107].More recently, a multi-center prospective study revealed that prophylactic DLI followed by MRD test and GVHD-guided multiple DLIs achieved a striking three-year LFS of 50% among 100 patients with refractory/relapsed AL [11].The successful use of pDLI in the haploidentical setting and risk-adjusted multiple pDLI represent a great step forward for advanced leukemia patients receiving allotransplant.

NK cell infusion

Regarding novel cellular therapy, Choi et al.[112] reported that a significantly higher DFS was observed in patients with additional NK cell infusion early after haplo-HSCT compared with their historical cohort who only received haplo-HSCT. Ciurea et al. also demonstrated that infusing high doses of *ex vivo*-expanded NK cells after haploidentical HSCT was associated with significantly lower viral infections and low relapse rate post transplant [113].

Maintenance therapy

Targeted drug therapy, such as the abovementioned TKI [56] and HMA[114],used alone or in combination with other strategies, offers promising prophylaxis in the post-HSCT maintenance setting for advanced leukemia. A recent multi-center Chinese study observed that sorafenib before transplantation, sorafenib maintenance after transplantation, and their combined application could improve the outcomes for patients with FLT3-ITD AML [115].

Recommendations (Figure 3):

For cases with refractory or relapsed disease pre-transplantation, relapse prophylaxis should be performed.

A. Donor selection: Haploidentical donors should be referred in the absence of a matched donor or for those in urgent need of transplant, especially for AML patients with positive pre-transplant MRD.
B. Modulation of conditioning regimen: New drugs that have stronger antitumor activity and/or less toxicity could be incorporated into conditioning regimens;
C. Immunomodulation
    a. Early withdrawal of immunosuppression: It is suggested that the withdrawal of IS should be implemented carefully within 100 days after haploidentical HSCT, or within 60 days after UCBT or MSDHSCT;
    b. For Ph-negative leukemia, prophylactic DLI early after HSCT can be chosen for patients without active GVHD. Subsequent MRD test and GVHD-guided multiple DLIs are proposed;
    c. Cytokines and novel cellular immunotherapy: cytokines, such as IFNα and IL-2, can be utilized. NK cell infusions have entered clinical trials.
D. Targeted drugs: Prophylactic use of TKI for Ph^+ALL is considered for patients with myeloid and platelet recovery, even when the *BCR-ABL1* is negative. New drugs, such as sorafinib and demethylation agents, should enter clinical trials.
E. Patients with refractory or relapsed disease could be recommended for clinical trials to explore new methods, such as novel conditioning regimens, for relapse prophylaxis.

For patients who relapsed or converted to MRD-positive after prophylaxis, please see the recommendations for relapse treatment or intervention after allo-HSCT.

Summary and perspective

A major achievement of this consensus was to speed clinical investigation of relapse monitoring, prevention, and treatment strategies by both focusing on recent field advances to ripen the commonly used procedures and highlight ongoing

development of novel approaches. Risk stratification-directed post-HSCT relapse management system is strongly advocated. It is well understood that, given the paucity of high-quality evidence such as large RCTs addressing critical questions in post-HSCT relapse, the proposed consensus statements have limitations and differ from evidence-based recommendations [36]. With further research on the biological and immunological mechanism of post-transplant relapse and the accumulation of evidence-based data, we will periodically perfect and update the consensus. In summary, we hope that this consensus developed by Chinese doctors inspires the refinement of global clinical practice for relapse management after allo-HSCT.

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Conflict of Interest

The authors declare that they have no conflicts of interests.

Authors' contributions

All authors reviewed the literature and wrote first drafts of specific sections. WY and HXJ assembled the sections and wrote the final version of the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Recommendation for relapse treatment after allogeneic stem cell transplantation

Figure 2. Recommendation for preemptive therapy or intervention after allogeneic stem cell transplantation

Figure 3. Recommendation for relapse prophylaxis after allogeneic stem cell transplantation

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

	Tumor maker					Chemerism	
	Chromosomal banding	FISH	MFC	PCR	NGS	XY FISH	STR
Sensitivity	10^{-1}	10^{-2}	10^{-3} to 10^{-4}	10^{-5} to 10^{-6}	10^{-2}	10^{-2}	
Applicability	subtypes	subtypes	Difficulties with some abnormal monocytes	Non-recurrent abnormalities to be optimized	Optimal but with high price	Sex mismatched HSCT	All types

Abbreviation: FISH, fluorescence in situ hybridization; MFC, multiparameter flow cytometry; PCR, polymerase chain reaction; NGS, next-generation sequencing; STR, short tandem repeat

Table2.Studies of preemptive DLI after allo-HSCT

Author Ref. and year Number,n Follow-up	MRD Detection		Int	Group			Relapse			NRM			LFS/OS		
	AML/MDS Marker (n)	ALL marker (n)		MRD (+) Int (n)	MRD (+) Con (n)	MRD (-) (n)	MRD (+) Int (%)	MRD (+) Con (%)	MRD (-) (%)	MRD (+) Int (%)	MRD (+) Con (%)	MRD (-) (%)	MRD (+) Int (%)	MRD (+) Con (%)	MRD (-) (%)
Tan, *et al* 2014[91] N=15 1-Year[a]	LAIPs (7)	LAIPs (8)	DLI	15	NA	NA	0.0	NA	NA	6.3	NA	NA	NA/93.8	NA	NA
Wang *et al* 2014[19] N=92 2-Year[a]	*RUNX1-RUNX1T1,* (92)		mDLI	17	13	62	24.0	87.0	NA	NA	NA	NA	64.0/NA	0.0/NA	NA
Qin*et al* 2014[92] N=129 2-Year[a]	chimerism, (71)	chimerism, (58)	mDLI	24	23	82	37.5	73.9	0	8.3	4.3	8.5	54.2/NA	21.7/NA	91.5
Yan,*et al* 2012[4] N=814 3-Year[a]	*WT1* +LAIPs, (529)	*WT1* +LAIPs, (285)	mDLI	56	49	709	27.8	64.4	18.1	14.0	11.4	19.7	55.6/ 58.3	24.1/ 28.1	61.6/ 66.0
Mo, *et al* 2016[26] N=101 3-Year[b]	*WT1* +LAIPs, (69)	*WT1* +LAIPs, (32)	mDLI	101	NA	NA	39.5	NA	NA	9.6	NA	NA	51.7/NA	NA	NA
Mo, *et al* 2017[63] N=80 2-Year[b]	*WT1* +LAIPs, (44)	*WT1* +LAIPs, (36)	mDLI	80	NA	NA	35.0	NA	NA	6.2	NA	NA	58.8/NA	NA	NA
Rujkijyanon*et al* 2013[90] N=38 3-Year[b]	chimerism, (21)	chimerism, (17)	DLI	38	NA	NA	33.5/100 (responder/ Non-responder)	NA	NA	NA	NA	NA	OS80.2/0 (responder/ Non-responder)	NA	NA

Rettinger*et al* 2011[89] N=71 2-Year[a]	chimerism, (71)	DLI	13	7	50	54.0	100	12.0	0	0	8.0	46.0/NA	0/NA	80.0/NA

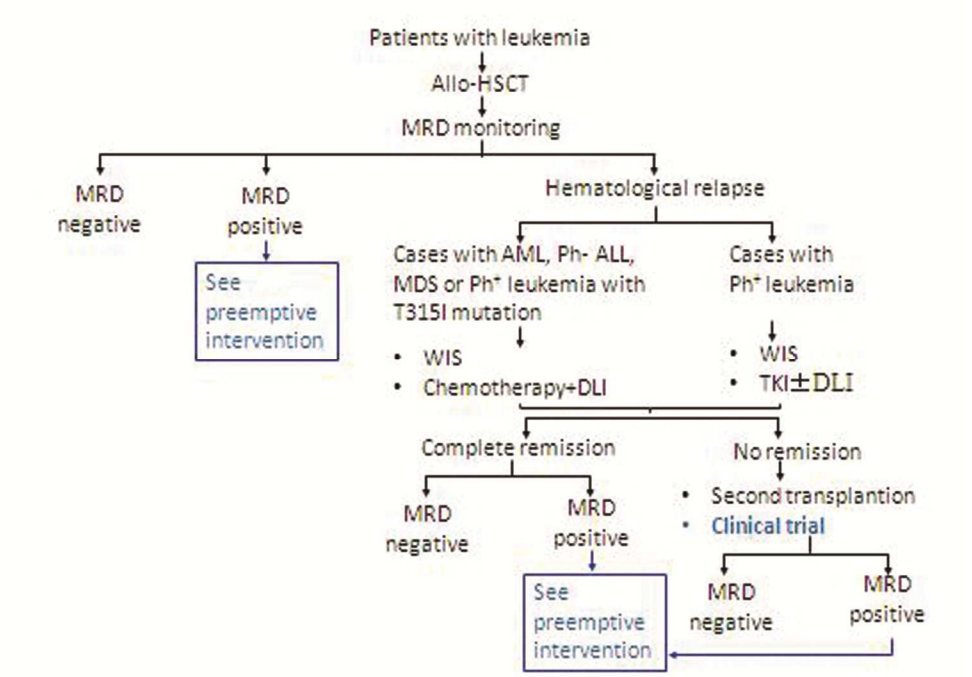
Abbreviation: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; Con, control; DLI, donor lymphocyte infusion; Int, intervention; LAIPs, leukaemia-associated immunophenotypic patterns; LFS, leukemia-free survival; mDLI, modified donor lymphocyte infusion; MDS, myelodysplastic syndrome; MFC,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

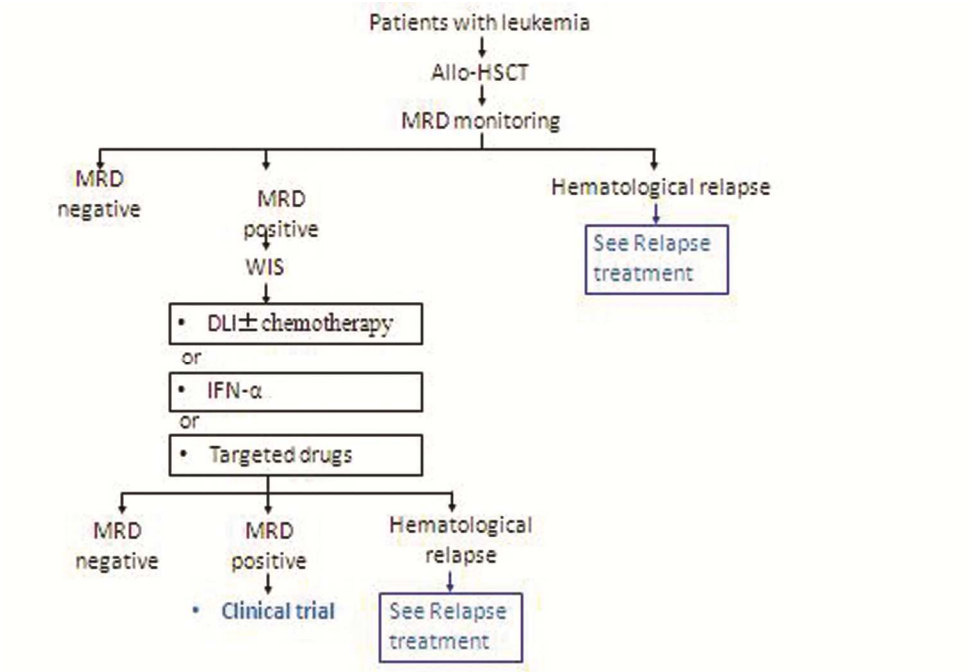
Table 3. Studies of prophylactic DLI after allo-HSCT

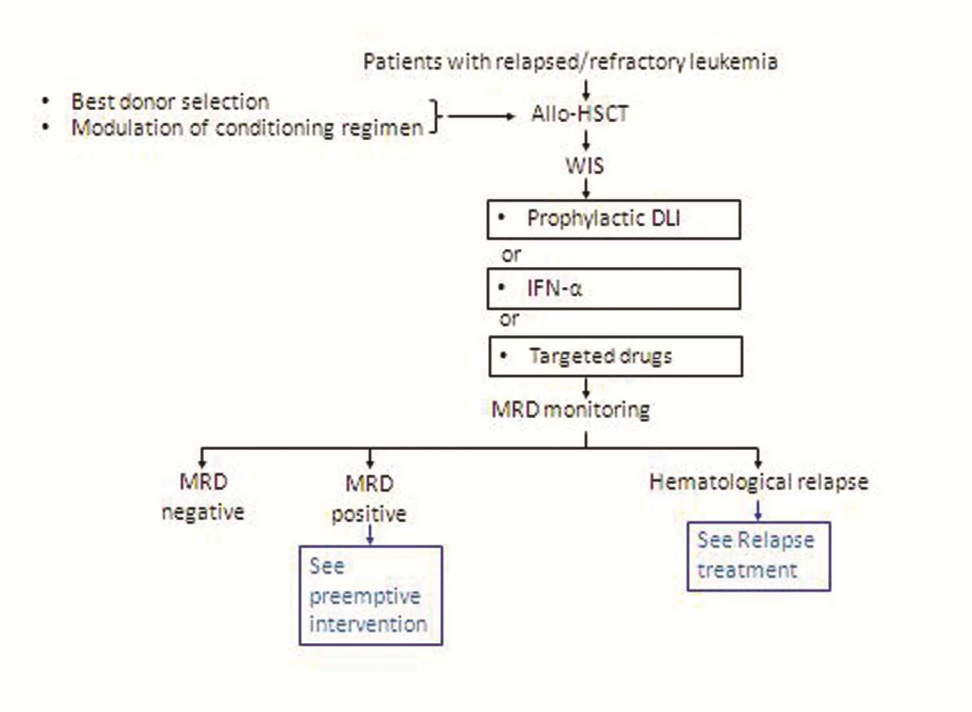
Author Ref. and year Number,n Follow-up	Disease		Donor	Int	Group		Relapse		NRM		LFS/OS	
	AML/MDS(n)	ALL (n)	type(n)		DLI+(n)	DLI-(n)	DLI+(%)	DLI-(%)	DLI+ (%)	DLI-(%)	DLI+ (%)	DLI-(%)
Schmid, *et al* 2005[105] N=75 2-Year[a]	75		MSD=31 HID=3 URD=41	DLI	12	NA	Total 27	NA	Total 33	NA	Total 40/42	NA
Huang, *et al* 2008[33] N=33 1.5-Year[a]	22	11	MSD=33	mDLI	33	NA	15/33	NA	3/33	NA	50.2/50.2	NA
Huang *et al*, 2008[32] N=29 3-Year[a]	16	13	HID=29	mDLI	29	NA	1y 51.3	NA	NA	NA	37.3/NA	NA
Schmid,*et al* 2012[106] N= 18 4-Year[a]	18		MSD=7 URD=11	DLI	8	NA	Total 22.2	NA	Total 23.5	NA	Total 54/61	NA
Wang, *et al* 2012[107] N=123 2-Year[a]	86	37	MSD=123	mDLI	50	73	46	66	20	20	3y 29/31	3y 9/11
Wang, *et al* 2012[29] N=88 2-Year[a]	54	34	HID=88	mDLI	61	27	36	55	38	33	3y 21/31	3y 11/11
Liga,*et al* 2013[110] N= 15	8	7	MSD=7 URD=8	DLI	15	NA	0	NA	4/15	NA	11/15	NA
Jedlickovaet *al* 2016[109] N=80 7-Year[a]	80		MSD=32 HID=2 URD=46	DLI	46	34	22	53	11	NA	6y 68/67	6y 38/31
Xuan, *et al* 2016[111] N=153 5-Year[a]	57	96	MSD=84 HID=41 URD=28	mDLI	80	64	22.7	33.9	NA	NA	57.2/58.1	47.3/54.9

Jaiswal*et al* 2016[108] N=41 1.5-Year[a]	41		HID=41	DLI	21	20	21	66	NA	NA	62/71	25/35
Yan*et al* 2017[11] N=100 1.5-Year[a]	59	41	MSD=36 HID=62 URD=2	mDLI	100	NA	32.4	NA	17.3	NA	50.3/51.4	NA

Abbreviation: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; DLI, donor lymphocyte infusion; Int, intervention; LFS, leukemia-free survival; mDLI, modified donor lymphocyte infusion; NA, not analyzed; NRM, non-relapse mortality; OS, overall survival; MSD, matched sibling donor; HID, haploidentical donor; URD, unrelated donor; a, time after transplantation; b, time after mDLI


Patients with leukemia
Allo-HSCT
MRD monitoring
MRD negative
MRD positive
See preemptive intervention
Hematological relapse
Cases with AML, Ph- ALL, MDS or Ph+ leukemia with T315I mutation
• WIS
• Chemotherapy+DLI
Cases with Ph+ leukemia
• WIS
• TKI±DLI
Complete remission
No remission
MRD negative
MRD positive
See preemptive intervention
• Second transplantion
• Clinical trial
MRD negative
MRD positive


Patients with leukemia
Allo-HSCT
MRD monitoring
MRD negative
MRD positive
WIS
Hematological relapse
See Relapse treatment
• DLI±chemotherapy
or
• IFN-α
or
• Targeted drugs
MRD negative
MRD positive
Hematological relapse
• Clinical trial
See Relapse treatment


Patients with relapsed/refractory leukemia
Best donor selection
Modulation of conditioning regimen
Allo-HSCT
WIS
Prophylactic DLI
or
IFN-α
or
Targeted drugs
MRD monitoring
MRD negative
MRD positive
Hematological relapse
See preemptive intervention
See Relapse treatment

Relapse remains the leading cause of death after transplantation.

Relapse management system in China is distinct from those in the Western world.

Summarized the consensus on routine practices of post-HCT relapse management in China

Focused on MRD monitoring, risk stratification directed strategies, and modified DLI

Contribute to the global standardization/refinement of post-HCT relapse management