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RESEARCH ARTICLE

Interferon-α salvage treatment is effective for patients with acute leukemia/myelodysplastic syndrome with unsatisfactory response to minimal residual disease-directed donor lymphocyte infusion after allogeneic hematopoietic stem cell transplantation

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Abstract **The efficacy of salvage interferon-α (IFN-α) treatment was investigated in patients with unsatisfactory response to minimal residual disease (MRD)-directed donor lymphocyte infusion (DLI) ($n = 24$). Patients who did not become MRD-negative at 1 month after DLI were those with unsatisfactory response and were eligible to receive salvage IFN-α treatment within 3 months of DLI. Recombinant human IFN-α-2b injections were subcutaneously administered 2–3 times a week for 6 months. Nine (37.5%), 6 (25.0%), and 3 (12.5%) patients became MRD-negative at 1, 2, and > 2 months after the salvage IFN-α treatment, respectively. Two-year cumulative incidences of relapse and non-relapse mortality were 35.9% and 8.3%, respectively. Two-year probabilities of event-free survival, disease-free survival, and overall survival were 51.6%, 54.3%, and 68.0%, respectively. Outcomes of patients subjected to salvage IFN-α treatment after DLI were significantly better than those with persistent MRD without IFN-α treatment. Moreover, clinical outcomes were comparable between the salvage DLI and IFN-α treatment groups. Thus, salvage IFN-α treatment may help improve the outcome of patients with unsatisfactory responses to MRD-directed DLI and could be a potential salvage treatment for these patients after allogeneic hematopoietic stem cell transplantation.**

Keywords interferon-α; hematopoietic stem cell transplantation; minimal residual disease; donor lymphocyte infusion

Introduction

Significant developments have been achieved in allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, post-transplant relapse remains a major cause of failure in transplantation. Minimal residual disease (MRD)-directed intervention, such as donor lymphocyte infusion (DLI), may be a viable option for relapse prophylaxis, because impending relapse can be indicated by MRD after allo-HSCT [1,2]. Previous studies indicated that the clinical outcome of MRD (+) patients receiving MRD-directed DLI was comparable to that of MRD (–) patients. The former had significantly better clinical outcome than MRD (+) patients who did not receive any interventions [3,4].

However, some patients exhibit persistent MRD after MRD-directed DLI, and this characteristic is associated with poor outcome. In our previous study, 18 of 93 patients did not achieve MRD (–) status after DLI, and 16 patients suffered relapse [5]. The cumulative incidence of relapse (CIR) after DLI was nearly 50% in those with persistent MRD at 1 month after DLI. In addition, multivariate analysis showed that persistent MRD at 1 month after DLI was associated with a significantly increased risk of relapse and poorer disease-free survival (DFS) compared with patients who became MRD (–) at 1 month after DLI [5].

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Thus, patients with persistent MRD after DLI showed unsatisfactory response to MRD-directed DLI. Clearance of MRD after DLI was critical to improve the outcome of these patients.

Several studies have shown that treatment with interferon-α (IFN-α) may be a feasible maintenance therapy for acute myeloid leukemia (AML) patients [6], and that IFN-α could exert a relatively strong immunomodulatory effect [7,8]. Moreover, IFN-α can induce the graft-versus-leukemia (GVL) effect and help acute leukemia patients who exhibit relapse after allo-HSCT attain complete remission (CR) [9–11]. We observed that MRD-directed IFN-α treatment was safe and effective for allo-HSCT recipients [12]. Moreover, salvage treatment with IFN-α helped eliminate MRD in patients who showed persistent MRD after DLI in our pilot study [13]. However, the sample size of this study was small ($n = 5$). Thus, whether IFN-α treatment and DLI show synergistic effects in MRD (+) patients remain ambiguous.

In this retrospective study, the efficacy of salvage treatment with IFN-α was investigated in patients with acute leukemia or myelodysplastic syndrome–refractory anemia with excess blasts (MDS-RAEB) who showed persistent MRD after MRD-directed DLI.

Materials and methods

Patients

Consecutive patients receiving non-T cell-depleted allo-HSCT at the Peking University Institute of Hematology were subjected to MRD-directed DLI if they met the following criteria: (1) MDS-RAEB or acute leukemia, defined as first or second CR without a Philadelphia chromosome; and (2) MRD (+) after allo-HSCT ($n = 67$). Patients who did not become MRD (–) 1 month after MRD-directed DLI were eligible to receive salvage treatment with IFN-α within 3 months of DLI. The key exclusion criteria for this treatment were as follows: active graft-versus-host disease (GVHD), active infection, severe myelosuppression, and organ failure. The final follow-up visits for endpoint analysis were conducted on February 28, 2017. Informed consent was obtained from all patients or the patients' guardians. The study was conducted in accordance with the *Declaration of Helsinki*. The study protocol was approved by the Ethics Committee of Peking University People's Hospital.

Transplant regimen

Preconditioning consisted of cytarabine (Ara-C), busulfan, cyclophosphamide (CY), and simustine. Rabbit antithymocyte globulin was administered to the human leukocyte antigen (HLA)-haploidentical related donor (haplo-RD), and HLA-unrelated donor (URD) groups (Supplementary methods) [14,15]. Granulocyte colony-stimulating factor (G-CSF)-mobilized, fresh, unmanipulated bone marrow (BM), and peripheral blood harvests were infused into the recipients on the day of collection. In addition, patients received cyclosporine A (CSA), mycophenolate mofetil (MMF), and short-term methotrexate (MTX) as GVHD prophylaxis [16]. Donor selection, HLA typing, and stem cell harvesting were performed as described previously [17].

MRD monitoring and definition

Patients were monitored for MRD post-transplantation according to leukemia-associated aberrant immune phenotypes (LAIPs) and genes. LAIPs were detected by multicolor flow cytometry (FCM). FCM positivity was considered when $> 0.01\%$ of cells showed an LAIP in post-transplantation BM samples [18]. The expression of leukemia-associated genes, including Wilms' tumor gene 1 (*WT1*) and the *RUNX1-RUNX1T1* translocation, were evaluated by TaqMan-based reverse transcription-polymerase chain reaction (RT-PCR). PCR-positivity for *RUNX1-RUNX1T1* was characterized as a $<$ 3-log reduction from the level at diagnosis and/or the loss of a $\geqslant$ 3-log reduction after 3 months post-HSCT [19,20]. *WT1* transcript level of $> 0.60\%$ was considered as positive [21]. Routine MRD monitoring was performed at 1, 2, 3, 4.5, 6, 9, and 12 months post-transplantation and at 6-month intervals thereafter. The tests were repeated 2 weeks after positive FCM or PCR results were obtained. MRD (+) status was defined as FCM positivity in 2 consecutive BM samples within a 2-week interval, PCR positivity in 2 consecutive BM samples within a 2-week interval, or both FCM and PCR positivity in a single BM sample [22]. MRD status was also monitored at 1, 2, 3, 4.5, 6, 9, and 12 months post-DLI and at 6-month intervals thereafter.

MRD-directed DLI protocol

Patients with active acute GVHD (aGVHD), active chronic GVHD (cGVHD), active infection, or organ failure were excluded from DLI treatment, which was performed as described by Yan *et al*. [4]. G-CSF-mobilized peripheral blood stem cells were administered instead of the more common unstimulated donor blood lymphocytes. The median doses of mononuclear cells, $CD3^+$ cells, $CD4^+$ lymphocytes, $CD8^+$ lymphocytes, and $CD34^+$ cells per kilogram were 1.0 (0.8–2.3) $\times$ 10^8, 3.5 (0.2–7.7) $\times$ 10^7, 2.0 (0.1–5.2) $\times$ 10^7, 1.2 (0.1–3.2) $\times$ 10^7, and 0.4 (0.1–1.5) $\times$ 10^6, respectively. Sixty-five patients received antileukemic chemotherapy at 48–72 h before DLI [23]. The chemotherapy regimens for patients with AML or MDS were as follows: harringtonine, aclacinomycin, and Ara-C

(HAA), $n = 19$; AA, $n = 28$; HA, $n = 3$; or idarubicin and Ara-C, $n = 1$. By contrast, patients with acute lymphoblastic leukemia (ALL) were treated with MTX ($n = 9$) or CY, vincristine, daunorubicin, and prednisone (CODP, $n = 5$) (Supplementary methods). Patients received immunosuppressive drugs, such as CSA or MTX, to prevent GVHD after DLI. Patients who received DLI from an HLA-identical sibling donor (ISD) were administered CSA or MTX for GVHD prophylaxis for 4–6 weeks. Meanwhile, those who received DLI from a haplo-RD or a URD were administered CSA for GVHD prophylaxis for 6–8 weeks at the discretion of the attending physicians (and usually depending on the patient's GVHD status after DLI). The starting dosage of CSA was 2.5 $mg \cdot kg^{-1} \cdot d^{-1}$, which was adjusted to maintain a plasma concentration of > 100 ng/mL. MTX (10 mg) was intravenously administered on days 1, 4, and 8 and weekly thereafter for 2–6 weeks. Detailed information on DLI for ISD, haplo-RD, and URD HSCT recipients is shown in Supplementary Table 1.

Salvage intervention after MRD-directed DLI

Patients who were MRD (+) at 1 month after MRD-directed DLI were the patients with unsatisfactory response to DLI. These patients were closely monitored. These patients could receive salvage intervention within 3 months of DLI if they agreed and had no active GVHD or active infection. Salvage intervention included DLI and IFN-α treatment, and this intervention was primarily based on the intentions of the physicians and patients (Fig. 1).

Salvage IFN-α treatment protocol

Based on the MRD status post-DLI and clinical conditions, salvage IFN-α treatment was administered as an intervention therapy within 3 months post-DLI, before hematologic relapse. Recombinant human IFN-α-2b injections (Anferon; Tianjin Hualida Biotechnology Co., Ltd., Tianjin, China) were subcutaneously administered at dosages of 3 million units for patients older than 16

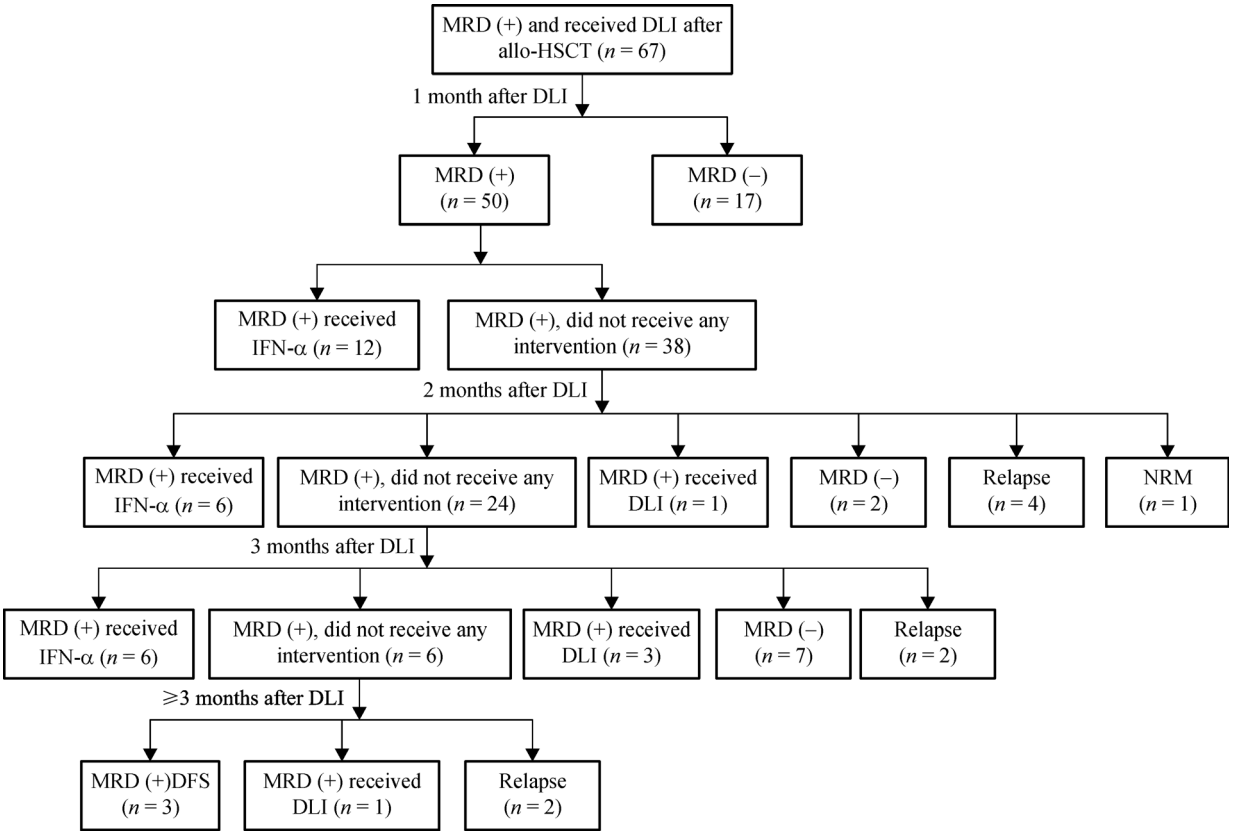

Fig. 1 Patients enrolled in this study. Patients who were minimal residual disease (MRD) (+) at 1 month after MRD-directed DLI were eligible to receive salvage interventions within 3 months of donor lymphocyte infusion (DLI), with consent, if they had no active graft-versus-host disease (GVHD) or active infection. Salvage interventions included treatment with IFN-α and DLI, and this intervention was primarily based on the physicians' and patients' intentions.

years and 3 million units per square meter (capped at 3 million units) for those younger than 16 years. These treatments were administered 2–3 times per week for 6 months. Prolonged treatment with IFN-α was permitted at patient's request. MRD status was monitored at 1, 2, 3, 4.5, 6, 9, and 12 months after salvage treatment and at 6-month intervals thereafter. Adverse events were scored using the National Cancer Institute Common Toxicity Criteria version 4.0 and monitored every 1–2 weeks after IFN-α treatment. GVHD was excluded as an adverse event. IFN-α treatment was discontinued in any patient with active severe GVHD, severe infection, toxicity grade of $\geqslant$ 3, a second round of DLI, relapse, or non-relapse mortality (NRM).

Patients who did not have active GVHD, active infection, and organ failure were eligible for a second round of DLI after salvage IFN-α treatment if they chose. These patients included those who regained MRD (+) status after achieving MRD (–) status or those with persistent and increasing MRD (from low-level MRD to high-level MRD) after salvage IFN-α treatment.

Salvage DLI treatment protocol

For patients who were MRD (+) at 1 month after MRD-directed DLI, salvage DLI could be administered within 3 months after the first DLI for those without GVHD. However, for those with GVHD after MRD-directed DLI, salvage DLI could be postponed until GVHD was resolved. The protocol was the same as that in the first round of DLI, and the doses of cells for infusion during salvage DLI were comparable to those during the first DLI (data not shown). Five patients received salvage DLI in the present study.

Treatment of GVHD after MRD-directed intervention

The treatment of GVHD was in accordance with the common international criteria [24,25].

Definitions and assessments

Disease risk at diagnosis was reported according to the criteria of Armand *et al*. [26]. GVHD after MRD-directed intervention was diagnosed according to the accepted international criteria [27,28]. Relapse was defined as morphologic evidence of disease in samples from the peripheral blood, BM, or extramedullary sites. Additionally, relapse was considered by the recurrence and sustained presence of pre-transplantation chromosomal abnormalities. Patients with MRD were not classified as relapse cases. NRM was defined as death without disease progression or relapse. Overall survival (OS) events were defined as death from any cause. DFS was the survival period with continuous CR. Event-free survival (EFS) events were relapse, death from any cause, or receipt of a second round of DLI after salvage IFN-α treatment. Early-onset MRD (EMRD) was characterized as MRD positivity $\leqslant$ 100 days after HSCT, while late-onset MRD (LMRD) was considered when MRD positivity $>$ 100 days after HSCT. High-level MRD was defined as a $\leqslant$ 2-log reduction in the *RUNX1-RUNX1T1* transcript level compared with that at diagnosis, *WT1* transcript levels of $\geqslant$ 1.0%, and/or LAIP positivity in $\geqslant$ 0.1% cells with LAIPs in the post-transplantation BM samples. The other cases were defined as low-level MRD.

Statistical analysis

All patients who received at least 2 weeks of study drug were included in the population. Data were censored at the time of the second round of DLI, relapse, NRM, or last available follow-up. Continuous variables were compared using Mann–Whitney U-test, while categorical variables were compared using the χ^2 and Fisher's exact tests. The probability of survival was estimated using Kaplan–Meier method. Competing risk analyses were performed to calculate the cumulative incidence of GVHD, relapse, and NRM using the Gray test to test for differences between groups [29]. Landmark day was the post-transplant day of the first MRD-directed DLI.

Potential prognostic factors for the 2-year clinical outcome after DLI were evaluated by multivariate analysis using Cox proportional hazards regression with a forward-stepwise model selection approach. The factors included in the regression model were underlying disease (AML/MDS vs. ALL), disease risk at diagnosis, donor type (ISD vs. non-ISD), time from allo-HSCT to MRD (EMRD vs. LMRD), MRD level prior to intervention (high vs. low), and MRD status and salvage IFN-α treatment after DLI [MRD (+) IFN (+) vs. MRD (+) IFN (–) vs. MRD (–)]. Independent variables with $P > 0.1$ were sequentially excluded from the model, and level of significance was set to $P < 0.05$. All reported *P*-values were based on two-sided tests. Data analyses were primarily conducted with SPSS software (SPSS Inc., Chicago, IL, USA), while R software package (version 2.6.1; http://www.r-project.org) was used for competing risk analysis.

Results

Patient characteristics

From January 1, 2013 to December 31, 2015, 24 patients were enrolled for salvage treatment (Fig. 1, Table 1). Full donor chimerism was detected in all MRD (+) patients. The median duration from DLI to IFN-α was 47 days (range, 30–95 days). The median duration of treatment was

80 days (range, 19–187 days). Eighteen patients received IFN-α treatment for < 6 months. IFN-α treatment was discontinued because of GVHD ($n = 8$), a second round of DLI ($n = 3$), relapse ($n = 4$), and a toxicity grade of ⩾ 3 ($n = 3$). The median duration of follow-up after DLI treatment was 556 days (range, 62–1336 days).

GVHD after IFN-α salvage treatment

Four patients developed aGVHD after the salvage IFN-α treatment, and grades II and III aGVHD were observed in two patients each. The median time from salvage IFN-α treatment to occurrence of aGVHD was 49 days (range, 29–56 days). The 2-year cumulative incidences of total and severe aGVHD (⩾ grade III) were 16.7% (95% CI, 1.4%–32.0%) and 8.3% (95% CI, 0.0%–19.6%), respectively.

Nine patients developed cGVHD after the salvage IFN-α treatment. Mild, moderate, and severe cGVHD were observed in 3, 2, and 4 patients, respectively. The median time from salvage IFN-α treatment to occurrence of cGVHD was 87 days (range, 22–283 days). The 2-year cumulative incidences of total and severe cGVHD were 37.5% (95% CI, 17.5%–57.5%) and 16.7% (95% CI, 1.4%–32.0%), respectively.

Toxicities and NRM after salvage IFN-α treatment

Three patients showed a toxicity grade of ⩾ 3, and 2 died of NRM after the salvage IFN-α treatment (severe pneumonia, $n = 1$; cerebral hemorrhage, $n = 1$). The 2-year cumulative incidence of NRM was 8.3% (95% CI, 0.0%–19.7%).

Relapse after salvage IFN-α treatment

Eight patients showed relapse after the salvage IFN-α treatment. The 2-year CIR was 35.9% (95% CI, 14.8%–57.0%), which was comparable between patients with AML/MDS and ALL (Fig. 2A).

Eighteen (75.0%) patients became MRD (–) after the salvage IFN-α treatment, with 9 (37.5%), 6 (25.0%), and 3 (12.5%) patients achieving this status 1, 2, and > 2 months after treatment, respectively. Six (25.0%) patients did not become MRD (–) after salvage IFN-α treatment, and 3 of whom had relapsed. The 2-year CIRs were 20.5% and 51.3% in patients who became MRD (–) and those with persistent MRD after salvage IFN-α treatment, respectively ($P = 0.131$, Fig. 2B).

EFS, DFS, and OS after salvage IFN-α treatment

Three patients were administered a second round of DLI after the salvage IFN-α treatment (2 patients became MRD (+) again after achieving MRD (–) status; 1 patient showed persistent and increasing MRD). The 2-year probability of EFS was 51.6% (95% CI, 29.7%–73.5%). This value was comparable between patients with AML/MDS and ALL and significantly higher in patients who became MRD (–) than those with persistent MRD after salvage IFN-α treatment (79.5% vs. 25.6%, $P = 0.011$; Supplementary Fig. 1A and 1B).

The 2-year probability of DFS was 54.3% (95% CI, 31.9%–76.7%). This value was comparable between patients with AML/MDS and ALL, as well as significantly higher in patients who became MRD (–) than in patients with persistent MRD after the salvage IFN-α treatment

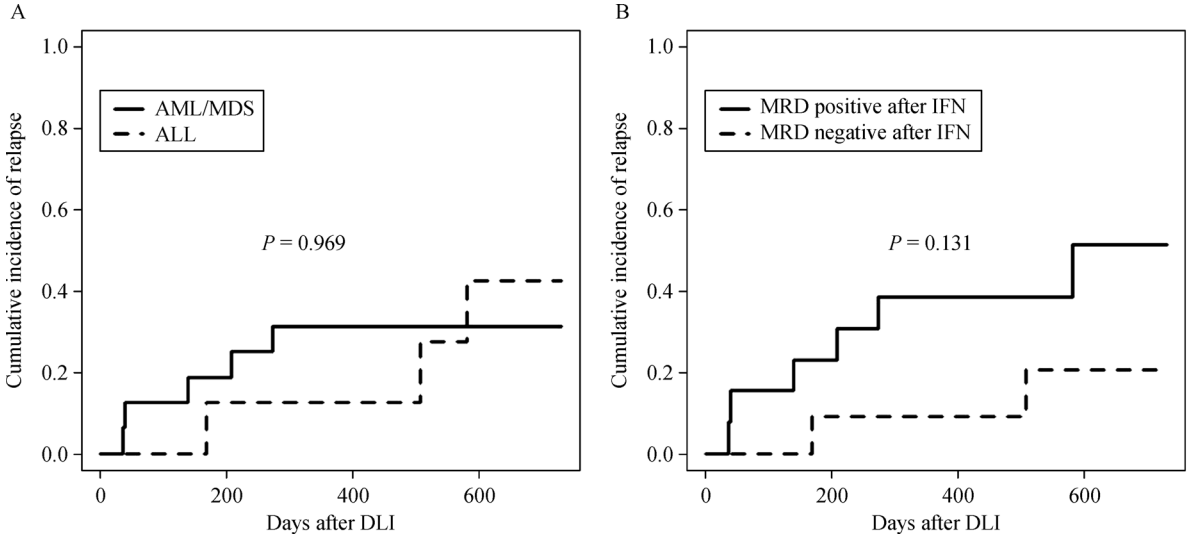

Fig. 2 Cumulative incidence of relapse at 2 years based on the (A) underlying disease (42.5% vs. 31.3%, $P = 0.969$) and (B) MRD status after salvage treatment with IFN-α (20.5% vs. 51.3%, $P = 0.131$).

(79.5% vs. 28.5%, $P = 0.019$; Supplementary Fig. 2A and 2B).

The 2-year probability of OS was 68.0% (95% CI, 47.3%–88.7%). This value was comparable between the AML/MDS and ALL patients, as well as between patients who became MRD (–) and with persistent MRD after salvage IFN-α treatment (79.5% vs. 59.2%, $P = 0.179$; Supplementary Fig. 3A and 3B).

None of the three patients who received a second round of DLI after the salvage IFN-α treatment became MRD (–). One relapsed, while the other two patients died of NRM.

Outcomes of patients with and without salvage IFN-α treatment after DLI

Two groups of patients did not receive salvage IFN-α treatment after MRD-directed DLI. Twenty-six patients became MRD (–) after DLI without additional treatment [MRD (–) group]. Seventeen patients showed persistent MRD at 1 month after DLI without salvage IFN-α treatment (5 received salvage DLI) [MRD (+) IFN (–) group]. We compared the clinical outcomes between these patients and those with persistent MRD who received salvage IFN-α treatment [$n = 24$, MRD (+) IFN (+) group]. Patient characteristics across the three groups are summarized in Table 1. The 2-year cumulative incidence of NRM after DLI was comparable among the three groups. The 2-year CIR and probability of DFS after DLI in the MRD (+) IFN (+) group were significantly better than in the MRD (+) IFN (–) group (CIR: 35.9% vs. 64.7%, $P = 0.007$; DFS: 54.3% vs. 29.4%, $P = 0.004$). The 2-year probability of OS after DLI in the MRD (+) IFN (+) group tended to be significantly better than in the MRD (+) IFN (–) group (68.0% vs. 41.7%, $P = 0.076$; Fig. 3A – 3D). In the subgroup analysis, the clinical outcomes were comparable between the patients who received salvage DLI ($n = 5$) and salvage IFN-α treatments (Relapse, 35.9% vs. 60.0%, $P = 0.129$; DFS, 54.3% vs. 40.0%, $P = 0.203$; OS, 68.0% vs. 75.0%, $P = 0.960$).

The results from the multivariate analysis indicated that salvage IFN-α treatment significantly decreased the risk of relapse and improved the DFS of MRD (+) patients after DLI, compared with MRD (+) patients who did not receive salvage IFN-α treatment (Table 2).

Discussion

Among patients who were MRD (+) at 1 month after MRD-directed DLI, the 2-year CIR and probability of DFS were both significantly improved in patients who received salvage IFN-α treatment after DLI. In addition, multivariate analysis suggested that salvage IFN-α could significantly decrease the risk of relapse and improve the DFS of these patients. Therefore, this study provides an opportunity to explore the currently undefined role of salvage IFN-α treatment in patients with unsatisfactory responses to MRD-directed DLI after allo-HSCT.

Although DLI is an effective immunotherapy for MRD after allo-HSCT, some patients exhibit persistent MRD after DLI. This phenomenon is significantly associated with increased risk of relapse and poorer survival [5,12]. In the present study, 12 patients who were MRD (+) after DLI did not receive further intervention. However, 8 of these patients showed relapse, and 6 of whom within 3 months of DLI. Thus, further clearance of MRD after DLI is critical to improve the outcome of these patients. *In vivo* and *in vitro* studies have shown that IFN-α treatment can kill leukemia cells [30,31]. We observed that IFN-α treatment could decrease the risk of relapse and improve the survival of MRD (+) patients [32]. Thus, IFN-α may have a synergistic effect with DLI. The efficacy of combined treatment with IFN-α and DLI had been observed in cases of recurrent chronic myeloid leukemia after allo-HSCT [33,34]. In addition, in our pilot study, all five patients with acute leukemia and unsatisfactory response to DLI who received salvage IFN-α treatment had significantly reduced or resolved MRD [13]. In the present study, the 2-year CIR of patients who received salvage IFN-α treatment was significantly lower than those with persistent MRD who did not receive salvage IFN-α treatment.

Moreover, cGVHD was more common in the MRD (–) group. This condition is closely related to the GVL effect [35,36], which is also important for clearing MRD after DLI [5]. Thus, development of MRD-negativity after DLI without further intervention may be attributed to the strong GVL effect induced by DLI. The GVL effect was weaker in patients who showed persistent MRD after DLI. Thus, IFN-α treatment may further intensify the GVL effect, facilitating the clearance of leukemia cells.

Although salvage IFN-α treatment can help clear MRD in patients with persistent MRD after DLI, 25% patients still did not become MRD (–), and their clinical outcome was poor. The results suggest that patients who were non-responsive to both DLI and IFN-α treatment were resistant to the GVL effect. Thus, for these patients, methods that clear leukemia cells through different mechanisms, such as azacitidine [37,38], natural killer cell infusion [39], T cells expressing a CD19-specific chimeric antigen receptor [40], and targeted drugs [41], are worth exploring.

Previous studies have shown the safety of preemptive IFN-α treatment after allo-HSCT [12,32,42]. In the present study, the 2-year NRM rate was 8.3%, which was comparable to the results from our previous studies (MRD-directed DLI: 4.4%–14.4% [4,5,12]; IFN-α treatment: 4.3%–4.5% [12,32]). This value was also comparable to the 2-year NRM rate of patients who became MRD (–) after DLI without further intervention. Severe aGVHD is one of the most significant causes of NRM after post-HSCT immunotherapy. The incidence of patients with ⩾

Table 1 Patient characteristics

Characteristics	MRD (–) group ($n = 26$)	MRD (+) IFN-α (+) group ($n = 24$)	MRD (+) IFN-α (–) group ($n = 17$)	P value
Median age at allo-HSCT, years (range)	28 (8–58)	23 (3–48)	28 (2–50)	0.478
Median time from allo-HSCT to DLI, days (range)	177 (79–821)	242 (63–1239)	214 (73–1552)	0.444
Underlying disease, *n* (%)				
Acute myeloid leukemia	13 (50.0)	15 (62.5)	11 (64.8)	0.338
Acute lymphoblastic leukemia	7 (26.9)	8 (33.3)	3 (17.6)	
Myelodysplastic syndrome	6 (23.1)	1 (4.2)	3 (17.6)	
Disease risk at diagnosis, *n* (%)				
Low risk	2 (7.7)	3 (12.5)	1 (5.9)	0.484
Intermediate risk	18 (69.2)	19 (79.2)	15 (88.2)	
High risk	6 (23.1)	2 (8.3)	1 (5.9)	
Sex, *n* (%)				
Male	14 (53.8)	14 (58.3)	11 (64.7)	0.779
Female	12 (46.2)	10 (41.7)	16 (35.3)	
Donor–recipient sex match, *n* (%)				
Female–male	6 (23.1)	7 (29.2)	2 (11.8)	0.430
Others	20 (76.9)	17 (70.8)	15 (88.2)	
ABO matched, *n* (%)				
Matched	15 (57.7)	12 (50.0)	10 (58.8)	0.811
Mismatched	11 (42.3)	12 (50.0)	7 (41.2)	
Donor–recipient relationship, *n* (%)				
Father–child	9 (34.6)	9 (37.5)	7 (41.2)	0.675
Mother–child	1 (3.8)	3 (12.5)	0 (0.0)	
Sibling–sibling	13 (50.0)	11 (45.8)	9 (52.9)	
Other related donor	3 (11.6)	0 (0.0)	0 (0.0)	
Unrelated donor	0 (0.0)	1 (4.2)	1 (5.9)	
Donor type, *n* (%)				
HLA-identical sibling donor	8 (30.8)	6 (25.0)	6 (35.3)	0.734
HLA-haploidentical related donor	18 (69.2)	17 (70.8)	10 (58.8)	
HLA-unrelated donor	0 (0.0)	1 (4.2)	1 (5.9)	
Number of HLA-A, HLA-B, HLA-DR mismatches, *n* (%)				
0	8 (30.8)	7 (29.2)	6 (35.3)	0.878
1	2 (7.7)	0 (0.0)	1 (5.8)	
2	2 (7.7)	2 (8.3)	2 (11.8)	
3	14 (53.8)	15 (62.5)	8 (47.1)	
MRD prior to preemptive DLI, *n* (%)				
Genetic markerpositive twice	15 (57.7)	11 (45.8)	5 (29.4)	0.175

(*Continued*)

Characteristics	MRD (–) group ($n = 26$)	MRD (+) IFN-α (+) group ($n = 24$)	MRD (+) IFN-α (–) group ($n = 17$)	*P* value
LAIPs positive twice	2 (7.7)	0 (0.0)	1 (5.9)	
Genetic marker and LAIPs positive simultaneous	9 (34.6)	13 (54.2)	11 (64.7)	
High-level MRD prior to DLI, *n* (%) [a]	21 (80.8)	17 (70.8)	15 (88.2)	0.411
Late onset MRD, *n* (%) [b]	18 (69.2)	16 (66.7)	13 (76.5)	0.789
Discontinuing immunosuppressions before DLI, *n* (%)	16 (61.5)	13 (54.2)	6 (35.3)	0.235
GVHD prophylaxis, *n* (%)				
Cyclosporine A	26 (100.0)	23 (95.8)	16 (94.1)	0.518
Methotrexate	0 (0.0)	1 (4.2)	1 (5.9)	
Subtypes of cells for DLI				
Median mononuclear cells, $\times 10^8$/kg (range)	1.0 (1.0–2.3)	1.0 (0.8–1.8)	1.0 (0.8–2.0)	0.558
Median $CD3^+$ counts, $\times 10^7$/kg (range)	3.6 (0.7–7.5)	3.3 (0.2–7.7)	3.5 (0.5–7.4)	0.565
Median $CD34^+$ counts, $\times 10^6$/kg (range)	0.3 (0.1–0.6)	0.4 (0.1–1.2)	0.5 (0.1–1.5)	0.064
Acute GVHD after DLI, *n* (%)	8 (30.8)	4 (16.6)	5 (29.4)	0.459
Grade I to II	5 (19.2)	2 (8.3)	3 (17.6)	0.570
Grade III to IV	3 (11.6)	2 (8.3)	2 (11.8)	1.000
Chronic GVHD after DLI, *n* (%)	19 (73.1)	9 (37.5)	7 (41.2)	0.024
Mild to moderate	7 (26.9)	5 (20.8)	5 (29.4)	0.824
Severe	12 (46.2)	4 (16.7)	2 (11.8)	0.021
Median follow-up after DLI, d (range)	532 (90–1231)	557 (62–1336)	190 (16–867)	0.017

allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; IFN-α, interferon-α; LAIPs, leukemia-associated immunophenotypic patterns; MRD, minimal residual disease.

[a]High-level MRD were defined as ⩽2-log reduction in the *RUNX1-RUNX1T1* transcript level from that at diagnosis, *WT1* transcript levels of ⩾1.0%, and/or LAIP positivity in ⩾0.1% cells with LAIPs in the post-transplantation BM samples; the other cases were defined as cases with low-level MRD.

[b]Early-onset MRD (EMRD) was defined as MRD becoming positive ⩽100 days after HSCT, and late-onset MRD (LMRD) was defined as MRD becoming positive >100 days after HSCT.

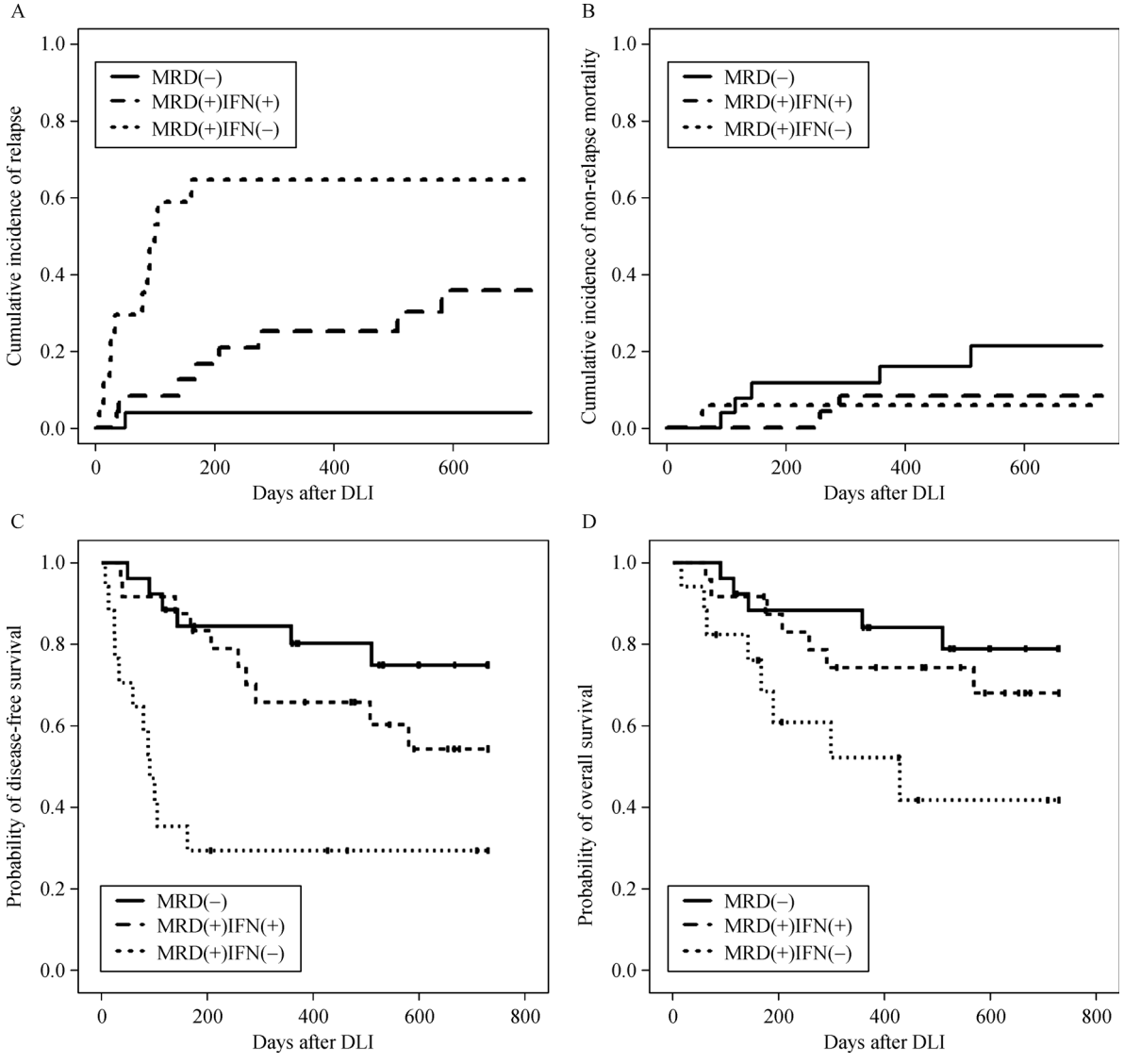

Fig. 3 Clinical outcomes of patients with and without exposure to salvage IFN-α treatment at 2 years after MRD-directed DLI. (A) Relapse: MRD (+) IFN (+) group vs. MRD (+) IFN (–) group: 35.9% vs. 64.7%, $P = 0.007$; MRD (+) IFN (+) group vs. MRD (–) group: 35.9% vs. 3.8%, $P = 0.011$; MRD (+) IFN (–) group vs. MRD (–) group: 64.7% vs. 3.8%, $P < 0.001$. (B) NRM: MRD (+) IFN (+) group vs. MRD (+) IFN (–) group: 8.3% vs. 5.9%, $P = 0.888$; MRD (+) IFN (+) group vs. MRD (–) group: 8.3% vs. 21.3%, $P = 0.233$; MRD (+) IFN(–) group vs. MRD (–) group: 5.9% vs. 21.3%, $P = 0.298$. (C) DFS: MRD (+) IFN (+) group vs. MRD (+) IFN (–) group: 54.3% vs. 29.4%, $P = 0.004$; MRD (+) IFN (+) group vs. MRD (–) group: 54.3% vs. 74.9%, $P = 0.206$; MRD (+) IFN (–) group vs. MRD (–) group: 29.4% vs. 74.9%, $P < 0.001$. (D) OS: MRD (+) IFN (+) group vs. MRD (+) IFN (–) group: 68.0% vs. 41.7%, $P = 0.076$; MRD (+) IFN (+) group vs. MRD (–) group: 68.0% vs. 78.8%, $P = 0.441$; MRD (+) IFN (–) group vs. MRD (–) group: 41.7% vs. 78.8%, $P = 0.015$.

grade III aGVHD was only 8.3% in the present study, which is also comparable to the result from our previous studies (MRD-directed DLI: 4.0%–8.2%; IFN-α: 4.5%–5.7%) [5,12,32,43].

This study had several limitations. First, this work was a retrospective study with a relatively small number of patients. Second, the observation period was relatively short. Finally, deriving conclusions about the superiority of salvage IFN-α treatment over salvage DLI in patients with unsatisfactory response to DLI is premature, because of the relatively small sample set who received salvage DLI. A randomized trial in the future will further compare the efficacy of these two salvage interventions.

In summary, salvage IFN-α treatment can help clear MRD and improve the clinical outcome of patients with unsatisfactory responses to MRD-directed DLI. The efficacy of this treatment should be further confirmed by large-scale and multicenter clinical studies.

Table 2 Multivariate analyses for 2-year clinical outcomes after DLI

	HR	95% CI	*P*
Relapse			
MRD (+) after DLI, without IFN-α	1.00		
MRD (+) after DLI, received IFN-α	0.28	0.11–0.70	**0.007**
MRD (−) after DLI	0.03	0.01–0.25	**0.001**
Treatment failure as defined by DFS			
MRD (+) after DLI, without IFN-α	1.00		
MRD (+) after DLI, received IFN-α	0.30	0.13–0.71	**0.006**
MRD (−) after DLI	0.14	0.05–0.39	**<0.001**
Treatment failure as defined by OS			
MRD (+) after DLI, without IFN-α	1.00		
MRD (+) after DLI, received IFN-α	0.41	0.15–1.13	0.085
MRD (−) after DLI	0.26	0.09–0.81	**0.020**

CI, confidence interval; DFS, disease-free survival; DLI, donor lymphocyte infusion; HR, hazard ratio; IFN-α, interferon-α; MRD, minimal residual disease; OS, overall survival.
None of variables was significantly associated with increased NRM. Underlying disease, disease risk at diagnosis, donor type, time from HSCT to MRD, and MRD level prior to DLI did not reach statistical significance in multivariate analysis. Bold font indicates statistical significance ($P < 0.05$).

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Compliance with ethics guidelines

Xiaodong Mo, Xiaohui Zhang, Lanping Xu, Yu Wang, Chenhua Yan, Huan Chen, Yuhong Chen, Wei Han, Fengrong Wang, Jingzhi Wang, Kaiyan Liu, and Xiaojun Huang declare no potential financial conflict of interest related to this manuscript. Informed consent was obtained from all patients or the patients' guardians. The study was conducted in accordance with the *Declaration of Helsinki*. The study protocol was approved by the Ethics Committee of Peking University People's Hospital.

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