Original Article

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PD-1 inhibitor in patients with minimal residual disease who failed donor lymphocyte infusion or interferon after allogeneic haematopoietic stem cell transplantation

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Abstract

This study aimed to evaluate the efficacy and safety of programmed death receptor 1 (PD-1) antibody in patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) with minimal residual disease (MRD) after allogeneic haematopoietic stem cell transplantation (allo-HSCT). Six patients were retrospectively reviewed in this study, and all had failed prior treatment (donor lymphocyte infusion or interferon) before PD-1 antibody administration. Among these 6 patients, two received PD-1 alone while four received PD-1 plus azacitidine. The median treatment with the PD-1 antibody was four doses (range, 1-7 doses). Three patients developed > grade 3 toxicity, including 2 deaths. Among the five evaluable patients, four achieved negative MRD with a median time to response of 2 months (range: 1-3 months); and the median duration of response was 105 days (range: 26-211 days). The median survival time of the five patients was 320 days (range: 107-350 days). Our data suggest that anti-PD-1 antibody in AML/MDS patients with positive MRD following allo-HSCT may be a treatment option.

Key words programmed death receptor 1 inhibitor, minimal residual disease, acute myeloid leukaemia, allogeneic hematopoietic stem cell transplantation

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Introduction

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the major curative treatment option for patients with hematologic malignancies[1]. However, relapse is one of the most important causes of HSCT failure. Approximately 20-40% of patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) relapse after HSCT. Once relapsed, salvage treatment options are limited, and the efficacy and survival rates are very low[2-5].

Minimal residual disease (MRD) is an excellent early warning biomarker of haematological relapse after HSCT[6,7]. MRD-based pre-emptive interventions can effectively reduce relapse rates and improve patient survival after HSCT. At present, pre-emptive intervention strategies for patients who are MRD-positive after transplantation mainly include donor lymphocyte infusion (DLI), interferons, targeted drugs, and alternative strategies[8-10]. However, for more than 22-39% of patients the above treatment methods are ineffective[11-14], and there are serious toxicity problems caused by the treatment, including graft-versus-host disease (GVHD), lung injury, and serious infection. Therefore, there is still an unmet need to find new MRD intervention strategies in clinical practice[15-17]. Clinical treatment is even more difficult in patients who have failed treatment or become MRD-positive again after the aforementioned interventions. Therefore, a novel treatment method is urgently needed.

It has been shown that immune escape is one of the possible mechanisms for relapse (either haematological or MRD relapse) after HSCT. The mechanisms of immune escape include downregulation of HLA gene expression or abnormal regulation of immune checkpoints[18]. Programmed death receptor 1 (PD-1) is an essential immune checkpoint inhibitory molecule on the surface of T cells, and its increased expression is a crucial mechanism leading to tumour immune escape[19,20]. Studies have shown that increased PD-1 expression is one of the mechanisms underlying the persistence of MRD and relapse after HSCT[21]. Theoretically, treatment with anti-PD-1 monoclonal antibodies (mAb) may be effective; however, data on MRD positivity after transplantation are lacking. In this study, we summarised the safety profile and preliminary efficacy of anti-PD-1 antibodies in patients with MRD after transplantation who failed DLI and/or interferon therapy.

Patients and Methods

Study design

This retrospective analysis included patients with AML or MDS who were MRD-positive after allo-HSCT and who received anti-PD-1 antibodies at Peking University People's Hospital between 1 January, 2022 and 31 March, 2022. According to expert consensus on ethical review exemption practices in medical institutions in China, it can be exempted from ethical review. All participants signed an informed consent document prior to enrolment in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Transplantation protocols

Patients who underwent haploidentical transplantation were pre-treated with a modified busulfan-based conditioning regimen, including cytarabine (4g/m^2/d) on days -10 to -9, busulfan (3.2 mg/kg/d) on days -8 to -6, cyclophosphamide (1.8 g/m^2/d) on days -5 to -4, oral semustine (250 mg/m^2) on day -3, and anti-thymocyte globulin (2.5 mg/kg/d) on days -5 to -2. Patients who received a human leukocyte antigen-matched sibling donor transplant received the same regimen as described above but without anti-thymocyte globulin. Granulocyte colony-stimulating factor (5 ug/kg/d for 5 days) was used to mobilise donor bone marrow and/or peripheral blood. Prophylaxis against GVHD consisted of the immunosuppressive agents, cyclosporin A, mycophenolate mofetil, and short-term methotrexate. The detailed method has been described in our previous publication[22].

MRD monitoring and intervention

MRD was monitored at 1, 2, 3, 4.5, 6, 9, and 12 months after allogeneic transplantation and at 6-month intervals thereafter. Both polymerase chain reaction (PCR) and multiparameter flow cytometry (FCM) were used to ensure the sensitivity and specificity of MRD monitoring. The expression of Wilms' tumour gene 1 or AML1-ETO was evaluated using real-time quantitative reverse transcription PCR, and ABL was selected as the control gene[23,24]. MRD positivity by FCM was defined when > 0.01% of cells showed leukaemia-associated aberrant immune phenotypes in bone marrow samples. PCR positivity for AML1-ETO was characterized as a < 3-log reduction from the level at diagnosis and/or the loss of a ≥ 3-log reduction after 3 months post-HSCT. For those without specific MRD biomarkers, MRD positive status was defined as two consecutive positive results detected by either FCM or PCR (Wilms' tumour gene 1 transcript level > 0.6%) with an interval of 10-14 days, or concurrent FCM-MRD positive and PCR-MRD positive in a single bone marrow sample[13,25]. For patients with MRD positivity, the therapeutic option of DLI or Interferon-alpha (IFN-α) was based on a DLI donor availability and the intentions of patients[25]. The IFN-α and DLI protocol was described in detail elsewhere[8,13].

The management of anti-PD-1 antibodies

Treatment with anti-PD-1 antibodies was considered in AML/MDS patients who met the following criteria: (1) MRD-positive status was confirmed after transplantation, (2) patients had refractory and recurrent MRD positivity after interferon or DLI therapy, and (3) there was no acute or chronic GVHD and no active infection before entering the study. Anti-PD-1 mAb (Tislelizumab, 240 mg every 2-3 weeks) administered alone or in combination with AZA (Azacitidine, 100 mg qd for 5-7 days) until disease progression or grade ≥ 3 nonhematologic toxicity occurred. Peripheral blood samples from healthy donors and from patients before and 2-3 weeks after treatment with the PD-1 mAb were collected, and the PD-1 expression levels on T cell subsets were measured by FCM. The monoclonal antibodies used included antihuman PD-1-PE-Cy7 (clone EH12.1) (BD Biosciences). T cells were divided into four subsets using the CD45RA and CCR7 expression: Naive T cells, CCR7+CD45RA+, central memory T cells CCR7+CD45RA-, effector memory T cells, CCR7-CD45RA- and effector T cells, CCR7-CD45RA+. The details have been described previously[26].

Efficacy assessment

(1) The treatment response was defined as at least a 1-log decrease in MRD results detected by multiplex

PCR or FCM after treatment compared to pre-treatment. (2) MRD negative was defined as the negative detection of MRD using PCR or FCM. (3) Overall survival was defined as the time from the date of anti-PD-1 mAb administration to the date of death due to any cause or the last follow-up date.

Safety assessment

The severity of treatment-related adverse events was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. The diagnosis and severity of chronic GVHD (cGVHD) were graded according to the Chinese Expert Consensus Guidelines (2021 edition)[27].

Follow-up

Follow-up was primarily conducted through outpatient visits and phone calls and ended on 8 February, 2023.

Statistical analysis

Safety was evaluated in all patients receiving anti-PD-1 mAb, and efficacy was evaluated in patients who underwent bone marrow aspiration at > 2 weeks after treatment. SPSS software (version 26.0 IBM Corp Armonk, NY USA) was used for the statistical analysis. Descriptive statistics were used to analyse the demographic and clinical characteristics of the patients.

Results

Patient characteristics

The patients' characteristics are summarized in **Table 1**. The median age of the six patients was 36 years (range: 26-38 years). Five patients were diagnosed with AML and one with MDS. Five patients underwent haploidentical transplantation, and one underwent HLA-matched sibling transplantation. Three patients were CR1- and MRD-negative at the time of transplantation and the remaining three were CR1- but MRD-positive.

MRD positive status and previous interventions prior to treatment with anti-PD-1 mAb

Three patients were positive for AML1/ETO PCR, and the level of AML1/ETO was above 0.1% and showed an upward trend before the administration of anti-PD-1 treatment. One patient was also positive by multiparameter flow cytometry. Of the six patients, the median interval from transplantation to the first MRD positivity was 135 days (range: 72-831 days). Four patients (66.7%) discontinued immunosuppressive agents after the first positive MRD, four patients (66.7%) received interferon therapy, and six patients (100%) received chemotherapy plus DLI. All patients had received two or more post-transplantation interventions prior to the anti-PD-1 mAb treatment.

Efficacy analysis

The median time from transplantation to the first dose of anti-PD-1 mAb was 796 days (range: 146-1,214 days) and the median time from the first MRD positivity to the first dose of PD-1 mAb was 430 (74-1,087) days (**Table 1**). Three patients were administered only one dose, two had four doses, and one had 7 doses. Two patients discontinued treatment due to severe GVHD, two due to disease progression, one due to a fatal side effect, and the remaining case due to coronavirus disease 2019 (COVID-19). One patient developed red maculopapular rash, pulmonary infection, and seizures after anti-PD-1 antibody treatment. Anti-infection and sedative treatment were given, but the patient died of sudden respiratory and cardiac arrest 5 days after anti-PD-1 antibody treatment and was excluded from the evaluation. Overall, four of the five evaluated patients (80%) achieved MRD negativity at a median of 2 months (range: 1-3 months) after a median of 3 doses (range: 1-5 doses), and the median duration of MRD negativity was 105 days (range: 26-211 days). Of the four patients with negative MRD, three tested positive again at 82, 90, and 316 days after treatment. One patient remained MRD-negative but had an extramedullary relapse. Of the five patients, one died of relapse, one died of cGVHD, and three survived. The patient with severe cGVHD of skin and liver died of progressive liver failure even after the administration of methylprednisolone, anti-CD25 monoclonal antibody and plasma exchange. At the last follow-up, the median survival time after anti-PD-1 mAb intervention was 320 days (range: 107-350 days).

Safety analysis

In this study, five of six patients experienced adverse events, with 50% grade 3-4 and one grade 5 adverse event. Common toxicities were myelosuppression, fever, and GVHD. Three patients developed grade 3 or 4 myelosuppression and five patients had fever, but all recovered spontaneously after withdrawal. Three cases were considered as cGVHD based on the typical manifestations of multiple organ involvement, liver involvement mainly with elevated bilirubin, and treatment response, one had moderate cGVHD and two had severe cGVHD. Two of the three patients showed improvement after treatment. The occurrence of immune-related adverse events (irAEs) after drug administration was 83%, mainly fever, including one case of immune-related thyroiditis. Clinical data for the six patients are presented in **Table 2** and adverse reactions to the anti-PD-1 mAb therapy are presented in **Table 3**.

Table 1. Baseline characteristics of patients (n=6)

Characteristics	results
Median age at transplant [years, M (range)]	36 (26-38)
Male [number (%)]	3 (50.0)
Disease diagnosis [number (%)]	
AML	5 (83.3)
MDS	1 (16.7)
Genetic abnormality [number (%)]	
AML1/ETO positive	3 (50.0)
TP53 mutation	1 (16.7)
Disease status at transplant [number (%)]	
CR1 with negative MRD	3 (50.0)
CR1 with positive MRD	3 (50.0)
Transplant modality [number (%)]	
MSDT	1 (16.7)
Haplo-SCT	5 (83.3)
MRD status before anti-PD-1 antibody treatment [number (%)]	
FCM+PCR-	2 (33.3)
FCM-PCR+	3 (50.0)
FCM+PCR+	1 (16.7)
Disease status before anti-PD-1 antibody treatment [number (%)]	
FCM positive with extramedullary relapse	1 (16.7)
Only FCM positive	1 (16.7)
AML1/ETO positive with PTLD	1 (16.7)
Only AML1/ETO positive	2 (33.3)
WT1 positive with extramedullary relapse	1 (16.7)
Interventions for MRD positivity before anti-PD-1 antibody treatment [number (%)]	
Reduction and withdrawal of immunosuppressive agents	4 (66.7)
Interferon	3 (50.0)
DLI	6 (100.0)
Time from transplant to first positive MRD [days, M (range)]	135 (72-831)
Time from transplant to anti-PD-1 antibody treatment [days, M (range)]	794 (146-1,214)
Time from first positive MRD to anti-PD-1 antibody treatment [days, M (range)]	430 (74-1,087)
Number of patients who responded to anti-PD-1 antibody treatment (%)	4/5 (80.0)
Number of patients with MRD negativity after anti-PD-1 antibody treatment (%)	4/5 (80.0)
Number of patients with MRD negative turned to positive after anti-PD-1 antibody treatment (%)	3/4 (75.0)
Duration of Response after anti-PD-1 antibody treatment [days, M (range)]	104 (26-290)
Duration of MRD-negativity after anti-PD-1 antibody treatment [days, M (range)]	86 (26-211)
Survival time after anti-PD-1 antibody treatment [days, M (range)]	320 (107-350)

AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; CR, complete remission; MRD, measurable residual disease; MSDT, matched sibling donor transplantation; haplo-SCT, haploidentical stem cell transplantation; PD-1, programmed death receptor 1; FCM, multiparameter flow cytometry; PCR, polymerase chain reaction; PTLD, post-transplant lymphoproliferative disease; DLI, donor lymphocyte infusion

Monitoring of PD-1 levels before and after administration of anti-PD-1 mAb

PD-1 expression on T cells in five patients before and 2-3 weeks after treatment with PD-1 mAb and in five healthy donors was measured by FCM. Higher expression of PD-1 on subsets of CD4+ T cells and CD4+ central memory T cells, CD4+ effector memory T cells, and CD4+ effector T cells were observed in patients with MRD positivity than in the healthy donor group (**Figure 1A**); this was not observed for CD8+T cells and their subsets (**Figure 1B**). After treatment with the PD-1 mAb, PD-1+ expression levels in CD4+ or CD8+T cells were significantly decreased, but there was no difference between patients who responded to the PD-1 antibody and those who did not (**Figure 1C, 1D**). The representative figure for flow cytometric analysis, the gating strategy, was shown in **Supplementary Figure 1**. The change in the proportion of total T cells, CD4 T cells, and CD8 T cells in the bone marrow change before and after PD-1 antibody treatment was shown in **Supplementary Table 1**.

Table 2. Clinical data of 6 patients with positive MRD after allogeneic transplantation treated with anti-PD-1 antibody

Program	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	male	female	male	female	female	male
Age (years)	26	38	38	36	35	36
Diagnosis	AML	AML	AML	AML	AML	MDS-U
Co-morbidities	none	Mixed tumor of lacrimal gland (after resection)	none	Chronic viral hepatitis B	none	none
Genes	Negative	EVI1	AML1/ETO	AML1/ETO KIT D816 mutation	AML1/ETO c-KIT mutation	TP53 mutation
Chromosomes	9q-	t(7;11)(p15;p15)	45,X,-Y,t(8;21)(q22;q22)	-	t (8;21)	-5,-7,add (17)
Transplant modality	Haplo-SCT	Haplo-SCT	Haplo-SCT	Haplo-SCT	MSDT	Haplo-SCT
Conditioning regimen	BU/CY+ATG	BU/CY+ATG	BU/CY+ATG	BU/CY+ATG	BU/CY	BU/CY+ATG
Neutrophil engraftment (days)	12	11	11	12	15	16
Platelet engraftment (days)	10	14	11	19	11	23
GVHD	-	Skin, degree I	-	-	-	-
Disease status before anti-PD-1 antibody treatment	FCM-MRD positivity with extramedullary relapse	MRD positivity with extramedullary relapse	PCR-MRD positivity with PTLD (ETO)	PCR-MRD positivity (ETO)	PCR-MRD positivity (ETO)	FCM-MRD positivity
Time from transplant to anti-PD-1 antibody treatment	+27 months	+26 months	+4.5 months	+7.5 months	+38 months	+40 months
Treatment regimen and number of courses	1 dose of anti-PD-1 antibody + AZA (100mg ×5 days)	4 doses of anti-PD-1 antibody + AZA (100mg ×7 days) + Ven (7 days)	4 doses of anti-PD-1 antibody +AZA (100mg ×7 days)	1 dose of anti-PD-1 antibody	7 doses of anti-PD-1 antibody	1 dose of anti-PD-1 antibody
Best response	MRD negativity	MRD negativity	MRD negativity	invalid	MRD negativity	-
Optimal duration of response (days)	180	26	30	-	211	-
Outcomes	died of disease recurrence	Survived without disease	died of severe GVHD	Survival (MRD positive)	Disease-free survival	died of neurological toxicity
Time from anti-PD-1 antibody to treatment switch or death (days)	205	85	107	71	320	11
PFS (days)	185	82	90	27	316	-
OS (days)	205	350	107	215	320	11

GVHD, graft-versus-host disease; PD-1, programmed death receptor 1; PFS, progression-free survival; OS, overall survival; BU, busulfan; CY, cyclophosphamide; ATG, anti-thymocyte globulin; MRD, minimal residual disease; FCM, multiparameter flow cytometry; AZA, azacitidine; BU, busulfan; Ven, Venetoclax; PCR, polymerase chain reaction; Haplo-SCT, haploidentical stem cell transplantation; MSDT, matched sibling donor transplantation; MDS-U, myelodysplastic syndrome-unclassifiable

Discussion

We report the preliminary data of anti-PD-1 mAb in six AML/MDS patients with recurrent positive MRD following allo-HSCT and multiple lines of treatment, including interferon, chemotherapy, and DLI intervention. These results demonstrate the safety and efficacy of anti-PD-1 mAb alone or in combination with AZA in AML/MDS patients with positive MRD following allo-HSCT.

Several studies[19,20] have shown that the PD-1 pathway is an immune escape mechanism of cancer stem cells after allogeneic transplantation. However, there are limited data on the safety and efficacy of immune checkpoint inhibitors in patients with myeloid neoplasms after transplantation. In animal models, PD-1 pathway blockade therapy has shown potent anti-leukaemic effects but is also associated with enhanced GVHD in xenografted nude mice[28]. Two retrospective cohort studies found that anti-PD-1 mAb also showed anti-tumour activity in Hodgkin's lymphoma that relapsed after transplantation but was also associated with severe and refractory GVHD[29,30]. The use of anti-PD-1 mAb in AML/MDS patients after transplantation has rarely been reported. Recently, a multicenter phase 1 study[31] of nivolumab for relapsed hematologic malignancies after

Table 3. Adverse effects of anti-PD-1 antibody treatment in 6 patients with positive MRD after allogeneic transplantation (NCI CTCAE version 5.0)

Adverse effects	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Neutropenia	Grade 3	-	Grade 4	Grade 2	-	-
Anemia	Grade 3	-	Grade 3	Grade 1	-	-
Thrombocytopenia	Grade 3	-	Grade 4	Grade 2	-	-
Elevated ALT grades	Grade 3	-	Grade 1	Grade 2	-	-
Elevated AST grades	Grade 3	-	Grade 3	Grade 1	-	-
Elevated total bilirubin	Grade 4	-	Grade 4	Grade 2	-	-
Fever	Grade 2	Grade 1	Grade 3	Grade 1	-	Grade 1
Pulmonary infection	Grade 3	-	-	-	-	Grade 1
Chronic GVHD	Severe	-	Severe	moderate	-	-
Rash	-	-	Grade 3	Grade 2	-	Grade 2
Hypothyroidism	-	-	-	-	-	Grade 1
Other infections	-	-	Grade 3 (Soft tissue)	-	-	-
Nervous system Epilepsy	-	-	-	-	-	Grade 5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GVHD, graft-versus-host disease

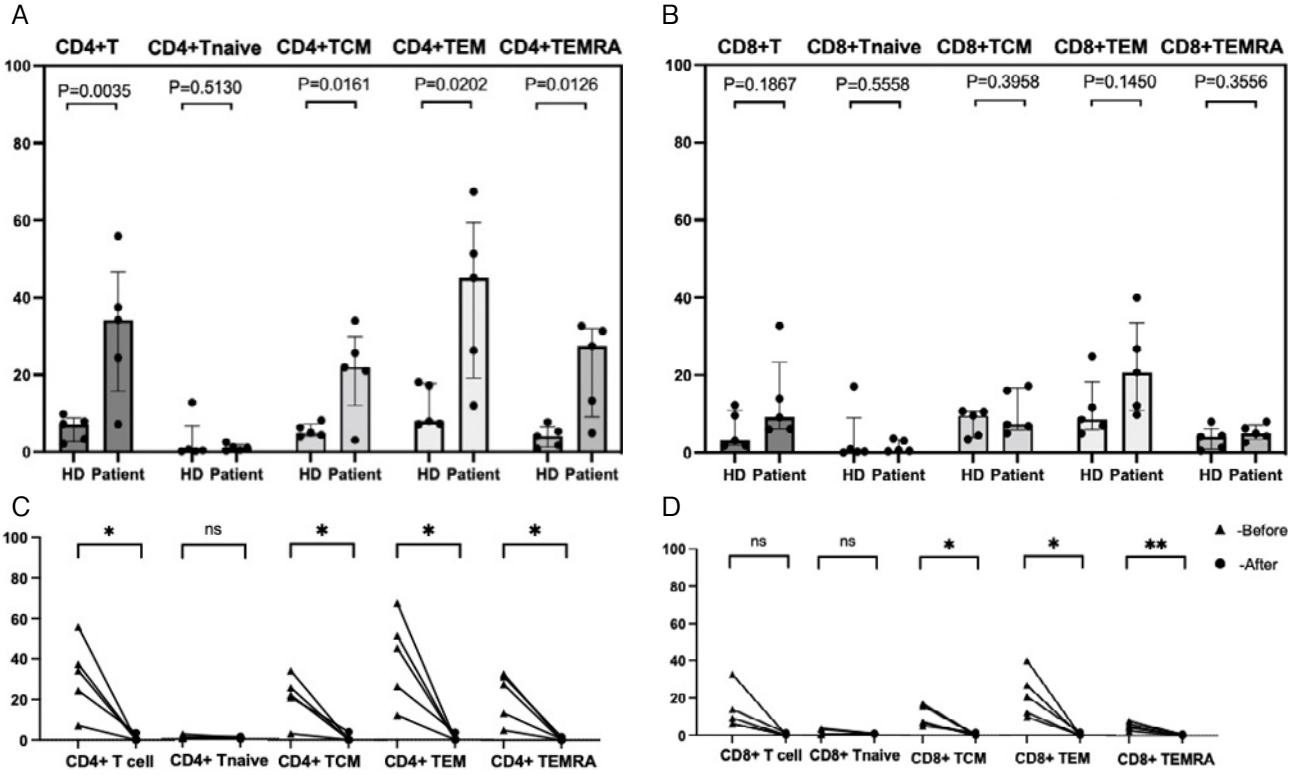

Figure 1. PD-1 expression on T cells
(A) PD-1 expression on CD4+ T cells and subsets in healthy donors (n=5) and in the patients with MRD positivity (n=5) groups. (B) PD-1 expression on CD8+ T cells and subsets in healthy donors (n=5) and in the patients with MRD positivity (n=5) groups. (C) PD-1 expression on CD4+ T cells before and after the PD-1 antibody treatment. (D) PD-1 expression on CD8+ T cells before and after the PD-1 antibody treatment.

allo-HSCT showed an objective response rate of 21% in nine patients with myeloid malignancies. Another prospective study[32] showed no objective response to pembrolizumab in nine patients with relapsed myeloid malignancies after allo-HSCT. Overall, the effect of monotherapy was poor. Qian et al.[33] reported two cases of anti-PD-1 mAb combined with AZA and low-dose DLI in the treatment of AML with haematological relapse after transplantation; both cases achieved complete remission, which lasted for 101 days and 257 days, re-

spectively. Tang et al.[34] reported that anti-PD-1 mAb combined with AZA were effective for the treatment of AML (AML1/ETO), with the first molecular relapse occurring after transplantation. In our study, six patients who remained refractory with recurrent positive MRD after transplantation, which was converted to positive after previous treatment with interferon, chemotherapy, and DLI while some had a haematologic relapse. Of the five evaluated patients, four responded and eventually achieved MRD negativity.

However, the duration of these responses was insufficient (28-294 days). In clinical trials of relapsed and refractory AML, the clinical effect of a PD-1 inhibitor as a single agent was poor; eight patients received a single dose of PD-1 inhibitor, and only one patient responded[35]. The escape mechanism of PD-1 inhibitor therapy includes the reduction of tumour antigen expression level, downregulation of the major histocompatibility complex, and loss of costimulatory ligand expression[36], while demethylation drugs can inhibit the immune response by upregulating the expression of PD-1, PD-L1, PD-L2, and CTLA-4[37], which is related to the emergence of drug resistance. Thus, the combined application of hypomethylating agents (HMA) and PD-1/PD-L1 inhibitors may exert stronger antitumour effects. In a phase II clinical trial[38], nivolumab (a PD-1 inhibitor) combined with AZA was evaluated in 70 AML patients with previous treatment failure (including HMA treatment). The overall response rate was 33%, which was 20% higher than that of relapsed/refractory-AML patients at centres that had previously participated in single-agent and combination HMA trials. The results showed that patients without previous HMA treatment exhibited a better response rate than those with previous HMA treatment (overall response rate, 58% vs. 22%). The frequency of bone marrow aspirate CD3 +T cells prior to AZA + nivolumab treatment was significantly higher than that in non-responders, and there was a trend toward higher frequencies of T effector and CD8+T cells. Several studies on the use of PD-1 inhibitors in combination with HMA for the treatment of AML/MDS are currently ongoing[39].

Studies have shown that patients with lymphoma who receive early PD-1 blockade therapy after allogeneic transplantation are more likely to develop GVHD[29,30]; however, the definition of "early" is unclear. A recent study encouraged drug use beyond 6 months after allo-HSCT for Hodgkin lymphoma[40]. However, another study found that in diseases other than Hodgkin lymphoma, the development of GVHD after allo-HSCT was not related to the time of initiation of immune checkpoint inhibitor therapy[41]. Qian et al.[33] reported two cases of anti-PD-1 mAb combined with AZA and low-dose DLI in the treatment of AML that relapsed after transplantation and showed that immune checkpoint inhibitor treatment did not appear to exacerbate or reactivate GVHD. Tang et al.[34] reported a case of low-dose anti-PD-1 mAb combined with AZA in the treatment of AML with molecular relapse after transplantation; the time from transplant to anti-PD-1 mAb treatment was 95 days and GVHD was observed, but was well controlled after treatment. In our study, three of six patients developed chronic GVHD. One patient treated 4.5 months after transplantation developed severe GVHD and died after ineffective treatment with multiple drugs. One patient developed moderate GVHD and responded to steroid and methotrexate therapies. The remaining patient also developed severe GVHD involving the liver but was effectively treated with cyclosporine, steroids, and CD25 mAb. Our limited case reports indicate that severe refractory GVHD is associated with the time interval between anti-PD-1 mAb therapy and transplantation.

Previous studies[26,42,43] have shown T cell exhaustion in patients with relapsed AML after transplantation, which can be reversed by DLI, and is associated with sustained complete remission[26]. This study showed that patients with MRD after transplantation also had T cell exhaustion, and treatment with a PD-1 mAb reduced the expression of PD-1 on the surface of T cells; however, no correlation was found between PD-1 expression and MRD negativity.

The limitations of this study included the limited number of cases and inadequate monitoring of adverse events, including non-specific reactions, such as fatigue and loss of appetite. In addition, we did not confirm that there was no competition between the therapeutic PD-1 antibody and the PD-1 antibody for expression evaluation, it was possible that the epitope was masked by the therapeutic PD-1 antibody when evaluating PD-1 expression after treatment.

Overall, the initial efficacy of anti-PD-1 monoclonal antibodies in the treatment of post-transplant MRD-positive myeloid neoplasms was positive, but their durability was modest. Additional studies are needed to determine whether unsatisfactory efficacy is associated with late intervention and the number of prior lines of treatment. The safety profile of anti-PD-1 mAb in the treatment of MRD-positive patients after allo-HSCT is acceptable, and its efficacy merits further exploration.

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Author Contributions

YQS and XJH designed the study, YQS revised the paper; LM collected the data, analyzed the data, and drafted the manuscript; all authors contributed to the data interpretation, manuscript preparation, and approval of the final version.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website. YQS is one of the editors of Blood Cell Therapy. He was not involved in the editorial evaluation or decision to accept this article for publication.

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Data Availability

The dataset supporting the conclusions of this article is available at the clinical data repository of Peking University People's Hospital and Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, No.11 South Street of Xizhimen, Xicheng District, Beijing, 100044, China.

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