Original Article

Teniposide-intensified hematopoietic stem cell transplantation with acute graft versus host disease prophylaxis with anti-thymocyte globulin provides good results in high-risk or refractory recurrent hematopoietic malignant diseases

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Background: Teniposide, as a more potent inhibitor of topoisomerase II compared with etoposide, shows less damage on hematopoietic stem cells. Few data are available on teniposide in hematopoietic stem cell transplantation (HSCT) for high-risk or refractory recurrent hematopoietic malignant diseases, particularly for acute myeloid leukemia (AML).

Methods: A retrospective single arm study was conducted to confirm the feasibility of teniposide (300 mg/m^2) -intensified HSCT in the treatment of high-risk or refractory recurrent hematopoietic malignant disease by analysing the outcomes of 32 patients, who received transplantation between January 2016 and December 2018. Univariate and multivariate analyses were performed to evaluate prognostic factors of the endpoints. Statistically significant factors ($P<0.05$) in multivariate analyses were regarded to be predictive.

Results: All patients achieved myeloid engraftment at a median of 13 days (range, 9–28 days), platelet engraftment at 15.5 days (range, 6–142 days), with a cumulative incidence (CI) of platelet engraftment of 93.75%±0.26%. The CI of grade II–IV acute graft versus host disease (aGVHD) was 43.75%±0.80% and that of grade III–IV aGVHD 12.50%±0.35%. The CI of chronic (c)GVHD was 74.07%±0.82% and that of extensive cGVHD 33.33%±0.87%. The CI of relapse was 35.03%±0.76%. The one-year probability of overall survival (OS) was 62.50%±0.09%, while 2-year OS was 46.90%±0.09%, and those of 1- and 2-year leukemia-free-survival (LFS) were 56.30%±0.09% and 46.90%±0.09%, respectively. Generally, the OS and LFS until the end of our follow up were 43.50%±0.09% and 34.80%±0.11%, respectively. The probability of GVHD-free and relapse-free survival (GRFS) was 24.60%±0.08%. Multivariate analysis indicated that the probability of OS was significantly lower in patients with a disease duration of more than 280 days before receiving HSCT and in those with fewer mononuclear cells. For LFS, other than the above two factors, failure to achieve complete response (CR) before HSCT was another independent risk factor. Similarly, the probability of GRFS was significantly lower in patients with longer disease duration (≥280 days) and those receiving stem cells from female donors.

Conclusions: For patients with high-risk or refractory recurrent hematopoietic malignant disease, teniposide-based conditioning regimens followed by allo-HSCT can be considered as an alternative therapy with encouraging prognoses.

Keywords: Teniposide; hematopoietic malignant diseases; hematopoietic stem cell transplantation (HSCT)

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Introduction

The treatment of high-risk or refractory recurrent hematopoietic malignant diseases, which are defined as a state of persistent leukemia with >5% blasts after at least 2 cycles of intensive induction therapy or hematologic relapse after initial clearance, including the detection of 5% or greater leukemic blasts in the bone marrow, the presence of blasts in the peripheral blood fulfills criteria for morphologic relapse, or the emergence of extramedullary disease, is one of the greatest challenges in medicine. With a disease-free survival of only approximately 30% to 40% after standard chemotherapy, disease persistence or recurrence occurs in most patients. The outlook for patients diagnosed as having high-risk or refractory recurrent hematopoietic malignant disease is poor, with a 3-year overall survival (OS) estimated at less than 10% (1,2). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment in patients with high-risk or refractory recurrent hematopoietic malignant disease (3,4). Nevertheless, relapse remains the most common causes of therapeutic failure in HSCT, particularly when treating patients with high-risk or refractory recurrent hematopoietic malignant disease (5,6). Studies based on nonmyeloablative (NMA) conditioning regimens report high relapse incidences and poor survival, especially for patients who fail to achieve complete remission at the time of transplantation (5,7-9). Intensification of myeloablative conditioning (MAC) seems to bring better tumor loading reduction with acceptable mortality during the transplantation process (9-11). Nonetheless, in patients transplanted with high-risk or refractory recurrent hematopoietic malignant disease, there is still scope for improvement. For the current study, we selected teniposide as a conditioning reginem to enhance prognosis.

Teniposide and etoposide are semisynthetic analogues of podophyllotoxin, and they are used in the treatment of leukemia, lymphoma, and certain sorts of solid tumors, usually in combination with other antineoplastic agents. Teniposide is a antineoplastic agent, which exerts its therapeutic effect by binding to and inhibiting topoisomerase II and, in addition, by preventing the healing of DNA breaks, which occur as a result of the action of topoisomerase II during cell replication (12). Furthermore, teniposide, as a more potent inhibitor of topoisomerase II compared with etoposide, shows less damage on hematopoietic stem cells. The dose-dependent antineoplastic activity of teniposide has advanced its use in conditioning regimens in HSCT for leukemias and lymphomas (13). However, to date, there have been no studies to determine whether teniposide-based conditioning regimens followed by allo-HSCT can be considered as an alternative therapy in the treatment of refractory recurrent hematopoietic malignant disease, particularly for acute myeloid leukemia (AML).

Here, we report on the outcomes of teniposide-intensified HSCT with GvHD prophylaxis with anti-thymocyte globulin (ATG) in high-risk or refractory recurrent hematopoietic malignant disease at our institution.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3122).

Methods

Patients

A retrospective single arm study was conducted to confirm the feasibility of teniposide (300 mg/m^2)-intensified HSCT in the treatment of high-risk or refractory recurrent hematopoietic malignant disease by following-up the patients meeting the inclusion criteria and analysing the outcomes. A total of 32 consecutive patients, who were diagnosed with high-risk or refractory recurrent hematopoietic malignant diseases and underwent teniposide-intensified HSCT with GvHD prophylaxis with ATG were enrolled through the Department of Hematology, Aerospace Center Hospital. Enrollment began on January 1, 2016, and ended on December 31, 2018, and the endpoint was defined as January 1, 2021, or death. Of the 32 consecutively recruited patients, one case was diagnosed with lymphoma, while five cases were diagnosed with acute lymphocytic leukemia (ALL), and 26 with AML. Four cases had undergone matched related-donor HSCT (MRD-HSCT), and 28 cases had undergone haploidentical HSCT (haplo-HSCT). The follow-up duration of alive patients was 1,007 days (range, 788–1,796 days). The research was approved by the institutional review board of Aerospace Center Hospital (No. 20200707-AMHTG-07), and written informed consent was obtained from all the subjects. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Conditioning regimen

The myeloablative conditioning regimens consisted of teniposide (300 mg/m^2), ATG plus other agents with

Table 1 Details of conditioning regimens

Conditioning regimens	N
VM26 + CLAG + BU + CY + ATG	4
VM26 + TBI + CLAG + ATG	3
VM26 + TBI + CLAG + ME-CCNU + CY + ATG	1
VM26 + BCNU + CLAG + BU + CY + ATG	1
VM26 + ME-CCNU + CLAG + BU + CY + ATG	3
VM26 + TBI + ME-CCNU + CY + ATG	1
VM26 + DAC + BU + CY + ATG	1
VM26 + DAC + Ara-C + BU + CY + ATG	1
VM26 + TBI + DAC + Ara-C + CY + ATG	1
VM26 + TBI + FLAG + ME-CCNU + ATG	1
VM26 + TBI + DAC + ME-CCNU + CY + ATG	1
VM26 + TBI + DAC + FLAG + ME-CCNU + BU + ATG	1
VM26 + Ara-C + BCNU + BU + CY + ATG	2
VM26 + TBI + RTX + BCNU + ATG	1
VM26 + TBI + FLAG + BCNU + ATG	2
VM26 + TBI + FLAG + ME-CCNU + ATG	2
VM26 + TBI + FLAG + BU + ATG	1
VM26 + TBI + Thiotepa + FLAG + BCNU + ATG	1
VM26 + TBI + 6-MP + BCNU + CY + ALG	1
VM26 + TBI + 6-MP + Ara-C + ME-CCNU + CY + ATG	1
VM26 + Ara-C + BU + CY + ATG	2

VM26, teniposide; CLAG, cladribine, cytarabine, and granulocyte colony stimulating factor; BU, Busulfan; CY, Cyclophosphamide; ATG, anti-thymocyte globulin; TBI, total body irradiation; ME-CCNU, semustine; BCBU, carmustine; DAC, decitabine; FLAG, fludarabine, cytarabine, and granulocyte colony stimulating factor; RTX, rituximab; 6-MP, 6-mercaptopurine.

either total body irradiation (TBI) or busulfan (*Table 1*). The applied chemotherapeutic agents including CLAG (cladribine, cytarabine, and granulocyte colony stimulating factor), cyclophosphamide, semustine, carmustine, decitabine, FLAG (fludarabine, cytarabine, and granulocyte colony stimulating factor), rituximab, 6-mercaptopurine.

Stem cell mobilization and collection

Thirty of the 32 patients received granulocyte colony-stimulating factor (G-CSF)-primed bone marrow (BM) combined with peripheral blood (PB) HSC, and the remaining two patients received only PB HSC from a haploidentical cousin and matched sister, respectively. Donor stem cell mobilization was performed using subcutaneous G-CSF (Filgrastim, Kirin, Japan or Granocyte, Chugai, Japan) at 5–10 μg/kg/day from day −3 until the last day of collection in patients who received both BM and PB HSCs, while for patients receiving PB HSCs solely, mobilization was brought forward to day −3. Bone marrow grafts were acquired on day 1. The target mononuclear cell (MNC) count from bone marrow was 2×10^8–4×10^8/kg recipient weight. Plasma reduction was performed in the case of minor Landsteiner's blood grouping system (ABO) incompatibilities, when donors had high-titer isoagglutinin exceeding 1:128, or recipients could not tolerate large volumes of infused plasma, while red blood cell count reduction was performed in those with major ABO incompatibilities. On day 2, peripheral blood stem cell (PBSCs) grafts were harvested by COBE Blood Cell Separator (Gambro BCT, Lakewood, CO, USA). The target MNC count was 8×10^8–10×10^8/kg recipient weight. Peripheral blood stem cells harvest was performed on the following day if the target was not achieved.

GVHD prophylaxis

Patients received GVHD prophylaxis including cyclosporine A (CsA) or tacrolimus for patients who were allergic to CsA, mycophenolate mofetil (MMF), or methotrexate (MTX). Cyclosporine A (1.25 mg/kg, q12h, intravenous) was administered from the start of the conditioning regime. Meanwhile, MMF (0.5 g, q12h) was administered orally when recipient bowel function remained normal, otherwise we switched drug delivery to intravenous. Methotrexate (15 mg/m^2, intravenous) was delivered on day +1, followed by a reduced dose (10 mg/m^2, intravenous) on days +3, +5, and +11 for haplo-HSCT, or followed by the same reduced dose on days +3 and +6 for MRD HSCT.

Definitions

Disease evaluation was defined according to standard criteria (14). Presence of refractory hematopoietic malignant disease was defined as bone marrow blasts >5% and/or the detection of extramedullary leukemia and/or manifestation of leukemic blasts in the peripheral blood after induction treatment (primary refractory hematopoietic malignant diseases) or, in the case of relapsed hematopoietic

malignant diseases, after intensive salvage therapy (secondary refractory hematopoietic malignant diseases).

Myeloid engraftment was defined as the first of three consecutive days when an absolute neutrophil count (ANC) $\geq 0.5\times10^9$/L was achieved, while platelet engraftment was defined as the first of seven consecutive days when a platelet count $\geq 20\times10^9$/L was achieved without transfusion. The primary endpoint was relapse. Secondary endpoints were GvHD, including acute (aGvHD) and chronic GvHD (cGvHD), OS, leukemia-free survival (LFS), and GvHD-free, relapse-free survival (GRFS). In our study, relapse was defined as the appearance of blasts in the peripheral blood or BM (>5%), and/or the detection of extramedullary leukemia after complete response (CR). Acute GvHD was graded according to the modified Seattle Glucksberg criteria (15) and cGvHD according to the revised Seattle criteria (16). LFS was calculated until the date of first relapse or death from any cause. Relapse-free survival was defined as survival without grade 3–4 acute GvHD, extensive cGvHD, relapse, or death after HSCT.

Statistical analysis

Mann-Whitney and chi-square tests were used for the analysis of continuous and categorical variables, respectively. The Kaplan-Meier method was used for log-rank tests, which were used for the time-to-event analyses (OS, LFS and GRFS). Cumulative incidences were used to estimate the competing risks of engraftment, GvHD, and early infection. Death was a competing risk for engraftment, GVHD, and early infection. Univariate and multivariate analyses were performed to evaluate prognostic factors of the study endpoints for selected factors. Continuous variables were divided into two groups on the basis of the medians. Factors with P<0.1 in univariate analyses were further evaluated in Cox multivariate regression models with a backward stepwise model selection approach. Statistically significant factors (P<0.05) in multivariate analyses were regarded to be predictive of outcomes. All statistical analyses were performed using SPSS Version 13.0 (IBM, Armonk, NJ, USA) and R software package (version 2.6.1; http://www.r-project.org).

Results

Basic characteristics

Detailed information regarding patient, disease, and transplantation characteristics are summarized in *Table 2*. The median follow-up of all patients was 479 days (range, 40–1,461 days), whereas for the survivors it was 1,007 days (range, 788–1,796 days). The most common diagnoses were AML (26 cases), followed by ALL (5 cases) and lymphoma (1 case). The median age at HSCT was 24.5 years (range, 3–55 years), and 23 patients (72%) were aged ≥18 years. Twenty-five patients (78%) were categorized as non-responders before HSCT. Most patients (28 of 32), received stem cells from haploidentical donors (14 fathers, 1 mother, 9 siblings, 2 children, and 2 collateral relatives) and four patients from MRD.

Engraftment

All patients achieved myeloid engraftment at a median of 13 days (range, 9–28 days). Platelet engraftment at 15.5 days occurred in 30 of 32 patients (range, 6–142 days), with cumulative incidences of platelet engraftment of 93.75%±0.26%.

GVHD

The cumulative incidence of grade II–IV aGVHD at 100 days was 43.75%±0.80% (*Figure 1*) and that of grade III–IV aGVHD was 12.50%±0.35% (*Figure 2*). The cumulative incidence of cGVHD was 74.07%±0.82% (*Figure 3*) and that of extensive cGVHD 33.33%±0.87% (*Figure 4*). Multivariate analysis identified no significant factors associated with either aGVHD or cGVHD (*Table 3*).

Survival outcomes

The cumulative incidence of relapse was 35.03%±0.76% (*Figure 5*). The 1-year probability of OS was 62.50%±0.09%, while the 2-year OS was 46.90%±0.09%, and the 1- and 2-year probability of LFS were 56.30%±0.09% and 46.90%±0.09%, respectively. The OS and LFS until the end of our follow-up were 43.50%±0.09% (*Figure 6*) and 34.80%±0.11% (*Figure 7*), respectively. Combining the survival outcomes and the cumulative incidence of GVHD, the probability of GRFS was 24.60%±0.08% (*Figure 8*) respectively.

In multivariate analyses (*Table 3*), the probability of OS was significantly lower in patients whose disease duration was more than 280 days before receiving HSCT [hazard ratio (HR) =0.147, 95% CI: 0.043–0.507, P=0.002] and in those with fewer MNC cells ($\leq 9\times10^8$/kg, HR =0.219,

Table 2 Patient characteristics

Variable	Value
Patients, n	32
Disease type, n	
AML	26
ALL	5
Lymphoma	1
Patient gender (male/female), n	13/19
Age	
Median [range], years	24.5 [3–55]
<18 years, n	9
≥18 years, n	23
Disease course	
Median [range], months	280.5 [90–816]
<280 d	15
≥280 d	17
Number of chemotherapy courses	
Median [range], times	4 [1–13]
≤4	17
>4	15
CNS leukemia pre-HSCT	
No	21
Yes	3
Leukemia status pre-HSCT	
CR	7
NR	25
HCT-CI, median [range]	1 [0–3]
≤1	29
>1	3
HLA matching type	
Haplo-HSCT	28
MRD HSCT	4
Donor source, n	
Father	14
Mother	1
Siblings	13
Child	2
Other	2
Donor-recipient gender, n	
Male to male	14
Male to female	14
Female to female	4
Donor gender, n	
Male	28
Female	4
Donor age	
Median [range], years	37 [10–58]
<37 years, n	16
≥37 years, n	16
Donor-recipient ABO match status	
Match	18
Minor mismatch	4
Major mismatch	8
Bidirectional mismatch	2
Number of MNC cells	
Median (range), $\times 10^8$/kg	9.01 (8.50–11.53)
$\leq 9\times 10^8$/kg	16
$>9\times 10^8$/kg	16
Number of $CD34^+$ cells	
Median (range), $\times 10^6$/kg	3.37 (0.80–8.07)
$\leq 3\times 10^6$/kg	13
$>3\times 10^6$/kg	19

ABO, Landsteiner's blood grouping system; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CNS, central nervous system; HCT-CI, hematopoietic cell transplantation-specific comorbidity; haplo-HSCT, HLA-haploidentical allogeneic hematopoietic stem cell transplantation; MRD, matched related donor; MNC, mononuclear cells.

95% CI: 0.073–0.653, P=0.006). For LFS, other than longer disease duration (≥280 days, HR =0.174, 95% CI: 0.054–0.555, P=0.003) and presence of fewer MNC cells ($\leq 9\times 10^8$/kg, HR =0.210, 95% CI: 0.068–0.644, P=0.006), failure to achieve CR before HSCT (HR =0.126, 95% CI: 0.017–0.962, P=0.046) was another independent risk factor. Similarly, the probability of GRFS was significantly lower in patients with longer disease duration (≥280 days, HR =0.263, 95% CI: 0.104–0.667, P=0.005) and those receiving

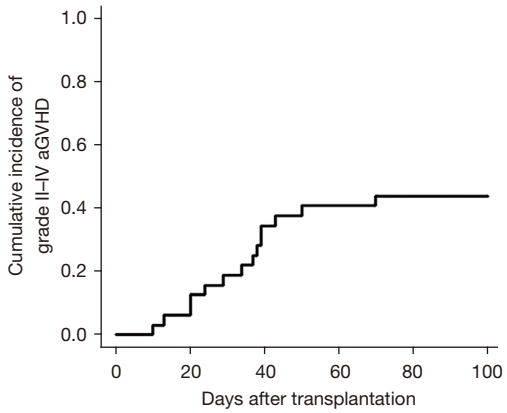

Figure 1 Cumulative incidence of grade II–IV acute graft versus host disease (%). aGVHD, acute graft versus host disease.

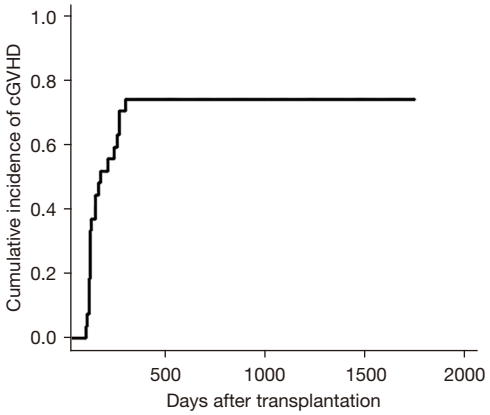

Figure 3 The cumulative incidence of chronic graft versus host disease. cGVHD, chronic graft versus host disease.

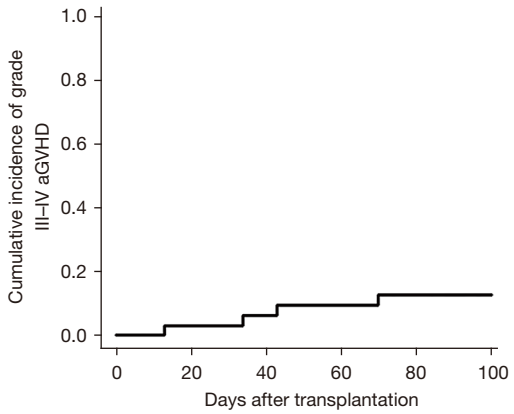

Figure 2 Cumulative incidence of grade III–IV acute graft versus host disease. aGVHD, acute graft versus host disease.

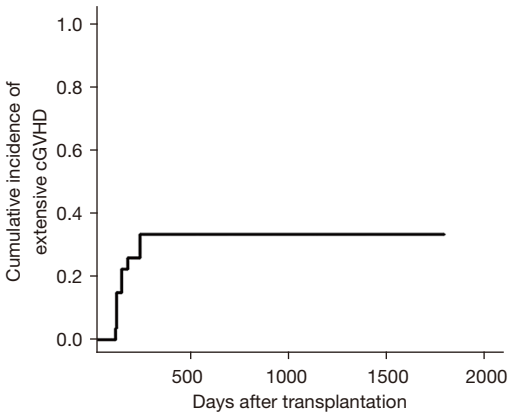

Figure 4 The cumulative incidence of extensive of chronic graft versus host disease. cGVHD, chronic graft versus host disease.

stem cells from female donors (HR =0.108, 95% CI: 0.029–0.397, P=0.001).

Discussion

To the best of our knowledge, we are the first to research and discuss the impact of a teniposide-intensified conditioning regimen on the outcomes of high-risk or refractory recurrent hematopoietic malignant disease in patients receiving HSCT. We achieved satisfactory results for OS and LFS, acceptable relapse rates, and GRFS, which was superior compared to most studies assessing high-risk or refractory recurrent hematopoietic malignant disease.

The treatment of high-risk or refractory recurrent hematopoietic malignant disease has a poor prognosis, and allo-HSCT may provide an effective method for affected patients. However, the prognosis after HSCT following common conditioning regimens is still disappointing (17-19). Therefore, the research on a variety of chemotherapeutics as conditioning regimens for allo-HSCT has been developing. Schmid *et al.* reported a prospective study on myelodysplastic syndrome (MDS) and high-risk AML. Fludarabine, cytarabine, and amsacrine were used for cytoreduction, followed by a conditioning regimen including 4 Gy total-body irradiation, antithymocyte globulin, and cyclophosphamide. Two-year OS and LFS achieved were 42% and 40%, respectively (20). Schmid *et al.* introduced a sequential conditioning regimen for patients with high-risk AML and MDS, consisting of fludarabine, cytarabine, and amsacrine, followed by reduced intensity conditioning, comprising 4 Gy total body irradiation, cyclophosphamide, and antithymocyte globulin. OS at 1, 2, and 4 years was

Table 3 Multivariate analysis of hazard factors

Outcomes	Hazard ratio (95% confidence interval)	P value
OS		
Disease course before HSCT (≥280 *vs.* <280 d)	0.147 (0.043–0.507)	0.002
Number of MNC cells (≤9×10^8 *vs.* >9×10^8/kg)	0.219 (0.073–0.653)	0.006
LFS		
Disease course before HSCT (≥280 *vs.* <280 d)	0.174 (0.054–0.555)	0.003
Tumor burden before HSCT (NR *vs.* CR)	0.126 (0.017-0.962)	0.046
Number of MNC cells (≤9×10^8 *vs.* >9×10^8/kg)	0.210 (0.068–0.644)	0.006
GRFS		
Disease course before HSCT (≥280 *vs.* <280 d)	0.263 (0.104–0.667)	0.005
Donor gender (female *vs.* male)	0.108 (0.029–0.397)	0.001

OS, overall survival; MNCs, mononuclear cells; LFS, leukemia-free survival; NR, non-remission; CR, complete remission; GRFS, graft versus host disease-free, relapse-free survival.

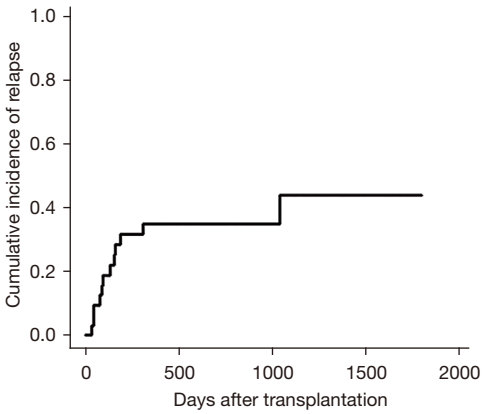

Figure 5 Cumulative incidence of relapse.

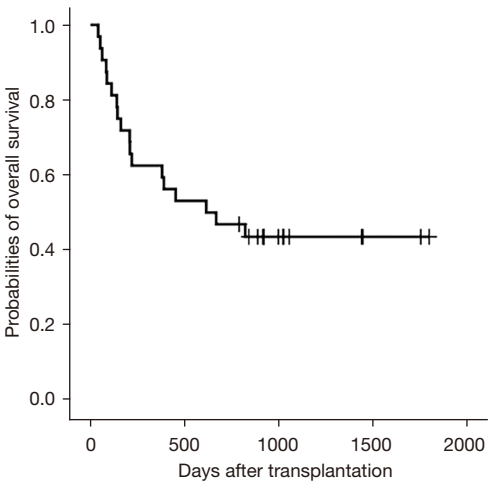

Figure 6 Probability of overall survival.

54%, 40%, and 32%, respectively; while LFS was 47%, 37%, and 30%, respectively (21). Steckel *et al.* reported that for adult patients with relapsed or refractory acute myeloid leukaemia, megadoses of melphalan-based conditioning chemotherapy followed by allo-HSCT enabled long-term remission to be achieved: 1- and 3-year OS were 46% and 34%, respectively. LFS 1 and 3 years after transplantation were 41% and 31%, respectively (22).

In our study on 32 patients with high-risk or refractory recurrent hematopoietic malignant disease treated with different teniposide-based conditioning regimens followed by allogeneic HSCT, the prognoses were encouraging, considering that OS was 43.50%±0.09% (follow-up period: 1,007 days; range, 788–1,796 days), while the 1-year probability of OS was 62.5%±0.09%, and the 2-year OS was 46.90%±0.09%, and those of LFS were 34.80%±0.11%, 56.30%±0.09%, and 46.90%±0.09%, respectively. Thus, the cumulative incidences of OS and LFS in our study were comparable, if not superior, to those published on comparable patient cohorts.

Teniposide, which shows a less toxic effect on hematopoietic progenitor cells, has been used in conditioning in HSCT for both leukemias and lymphomas (13). As early as in 1987, Krance *et al.* reported on a pilot regimen, which included teniposide. Ten patients with acute lymphoblastic leukemia in relapse underwent allo-HSCT. All patients engrafted. Toxicity and primary mucositis were manageable. Two patients survived for 1,547 and 1,988 days and continued

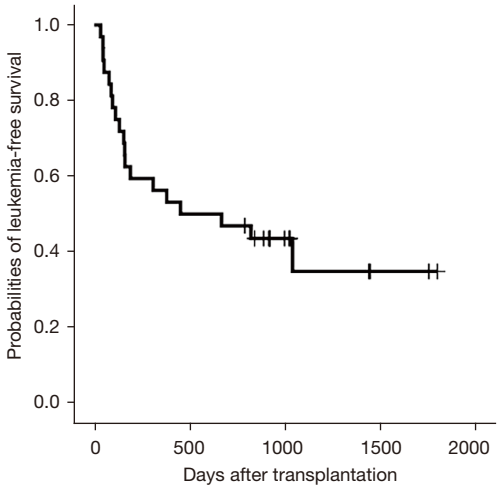

Figure 7 Probability of leukemia-free survival.

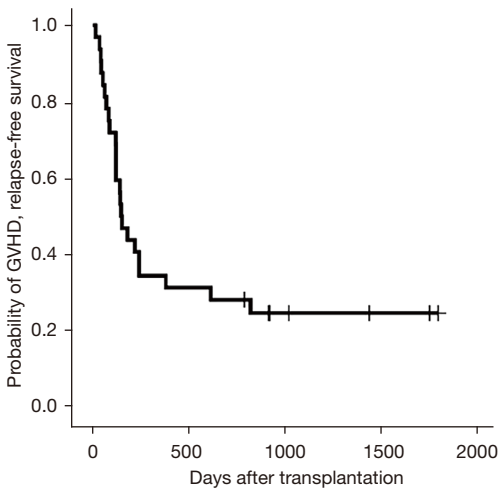

Figure 8 Probability of graft versus host disease-free, relapse-free survival. GVHD, graft versus host disease.

to be remission. Eight patients died: three from sepsis in the immediate posttransplant period, four from recurrent leukemia, and one from cGVHD and pneumonia (23). However, few data are available on teniposide in HSCT for high-risk or refractory recurrent hematopoietic malignant disease apart from the data reported here. Thus, selection of an ideal conditioning therapy appears to be a crucial step.

In our study, longer duration of illness (more than 280 days before receiving HSCT) and fewer MNC cells ($\leq 9\times10^8$/kg) were associated with inferior OS. For LFS, other than longer duration and fewer MNC cells, a higher tumor burden (patients who failed to achieve CR before receiving HSCT) was also an independent risk factor. Longer duration of illness before HSCT and having a female donor were factors related to poorer GRFS. These factors indicate that further attention to improve future transplantation strategies is required.

We found that tumor burden before receiving HSCT indicated unfavourable LFS outcomes, which is in accordance with previous research (1,24-26). However, to date, a large number of patients show incomplete response to induction chemotherapy or relapse after initial CR, and further salvage regimens are unlikely to significantly improve remission status for these patients (27,28). Moreover, as our study proved, the time before transplantation should be reduced for patients with high-risk or refractory recurrent hematopoietic malignant disease, because it increases the risk of leukemia cells becoming more resistant to available antineoplastic agents and the risk of accumulated damage to organ function, thus leading to inferior OS, LFS, and GRFS. Moreover, in most cases, more chemotherapy courses and longer disease duration before receiving HSCT are accompanied by increased thrombocytopenia and neutropenia with significant risks of bleeding and iron overload associated with excessive blood transfusion; notably, increased infection risks eventually cause fewer opportunitie for a disease-free outcome. Therefore, considering the disappointing response rates to salvage chemotherapies and their frequently unfavourable toxicity profiles, timely allogeneic transplantation to shorten the duration before HSTC, instead of more chemotherapy courses, has demonstrated the potential to superior survival outcomes for these patients.

Furthermore, our study found that fewer MNC cells ($\leq 9\times10^8$/kg) were associated with inferior OS and LFS, while having a female donor was an independent risk factor for GRFS, which is in accordance with many previous studies (29-31).

Our study has several limitations. It is retrospective and may be affected by the limited number of patients. Furthermore, as a single arm study, parallel comparison trial was absent, which appears to be insufficient to obtain a definitive conclusion. However, to achieve more precious results, we compared the outcomes with historical controlled studies.

In conclusion, firstly, our findings suggest that for patients with high-risk or refractory recurrent hematopoietic malignant disease, teniposide-based conditioning regimens followed by allo-HSCT can be considered an alternative therapy, with encouraging prognoses. Secondly, we suggest

that whenever feasible, excessive chemotherapy courses should be avoided for patients with insufficient response to induction therapy or relapse after CR, and receiving HSCT without delay for better prognosis. Thirdly, demand for adequate number of MNC cells (>9×10^8/kg) should be met in order to achieving superior OS and LFS. Finally, female donors should be avoided if possible to prevent inferior GRFS. Further studies with larger sample sizes are required to confirm these findings and assess the factors influencing clinical outcomes after HSCT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3122

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3122). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Aerospace Center Hospital (No. 20200707-AMHTG-07) and informed consent was taken from all the patients.

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