

Chidamide plus venetoclax as effective and safe maintenance therapy in high-risk acute myeloid leukemia and myelodysplastic syndrome post-transplantation

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Abstract

Relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the leading cause of treatment failure in high-risk acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), yet effective maintenance strategies are currently lacking. The combination of chidamide (CHI) and venetoclax (VEN) represents a novel approach. However, real-world data on its use are limited. In this study, eighteen high-risk transplant recipients received maintenance therapy with CHI (5 mg/day on days 1–7 or 1–14) plus VEN (100 mg on day 1, then 200 mg on days 2–7 or 2–14) every 2 months. Endpoints included overall survival (OS), disease-free survival (DFS), cumulative incidence of relapse (CIR), non-relapse mortality (NRM), and safety. After a median follow-up of 708 days, the 3-year OS and DFS were 68.6% and 48.8%, respectively. The 3-year CIR was 44.1%, and the 3-year NRM was 23.6%. The most common adverse events were hematologic, including neutropenia (13 episodes), thrombocytopenia (7), and anemia (7), all of which were manageable. No treatment-related mortality, tumor lysis syndrome, or severe acute graft-versus-host disease (GVHD) occurred. In conclusion, CHI plus VEN as post-transplant maintenance therapy shows encouraging efficacy and a manageable safety profile in high-risk AML/MDS patients, representing a promising strategy for relapse prevention.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) serves as a potentially curative option for patients with high-risk acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [1–3]. However, disease relapse remains the primary cause of treatment failure and mortality post-transplantation [4–6]. Patients who experience relapse face a dismal prognosis, with a median survival of only several months, posing a major challenge in current clinical practice [4–6]. Although maintenance strategies such as donor lymphocyte infusion and targeted therapies have been investigated to prevent relapse, their efficacy is often limited by an increased risk of graft-versus-host disease (GVHD), myelosuppressive toxicity, or inadequate response [5, 7]. Therefore, there is an urgent clinical need to develop novel maintenance therapies capable of effectively eliminating minimal residual disease (MRD) while maintaining a favorable safety and tolerability profile.

In recent years, significant progress in deciphering the pathological mechanisms of AML has accelerated the development of targeted and epigenetic therapies. Among these advances, the BCL-2 inhibitor venetoclax (VEN) has garnered considerable attention due to its potent anti-leukemic activity, which primarily functions by inducing apoptosis in tumor cells. As a result, VEN has emerged as a cornerstone agent in AML maintenance therapy, especially when used in combination with hypomethylating agents (Ven-HMAs) [8]. However, with the expanding clinical application of VEN-based therapies, the therapeutic efficacy of VEN is frequently compromised by primary resistance and clonal evolution. This limitation is particularly pronounced in certain AML subtypes, such as those exhibiting monocytic differentiation or specific genetic mutations, including alterations in *TP53*, *FLT3-ITD*, and *IDH*, which are consistently associated with suboptimal response rates and inferior clinical outcomes [9–13].

In contrast to VEN, the histone deacetylase inhibitor chidamide (CHI) acts by reversing epigenetic dysregulation and restoring the expression of tumor suppressor genes[14, 15]. CHI has demonstrated efficacy both as monotherapy and in combination with chemotherapy for relapsed/refractory AML(r/rAML) [16–18]. Notably, preclinical studies have revealed a marked synergistic effect between CHI and VEN in inducing apoptosis in AML cells[19, 20]. Mechanistically, CHI downregulates anti-apoptotic proteins such as MCL-1 and promotes DNA damage, thereby countering common resistance mechanisms observed with VEN [19, 20]. Moreover, this combination may enhance the graft-versus-leukemia (GVL) effect by modulating the immune microenvironment without increasing the risk of GVHD[19, 20]. Such mechanistic synergy provides a strong rationale for the combined use of CHI and VEN in the post-transplant maintenance setting. Nonetheless, clinical evidence regarding the efficacy, safety, and long-term outcomes of this combination after transplantation remains limited and warrants further validation through dedicated clinical studies.

In this study, we aim to systematically evaluate the real-world efficacy and safety of CHI combined with VEN as maintenance therapy following allo-HSCT in patients with high-risk AML/MDS, using a retrospective analysis. By analyzing clinical data from patients treated at our center, we seek to assess the efficacy of this combination in improving response rates and prolonging survival, while closely monitoring treatment-related toxicities and its impact on the risk of GVHD. The findings are expected to provide direct clinical evidence to support the use of this combination strategy in post-transplant maintenance therapy, thereby offering valuable insights for optimizing overall management and facilitating personalized treatment decisions in high-risk AML/MDS patients.

Patients and Methods

Patients

This study enrolled high-risk AML/MDS patients who were treated in the Department of Hematology at Tianjin First Central Hospital between February 2021 and March 2025. Based on comprehensive treatment data, specific inclusion and exclusion criteria were defined according to the research objectives.

Inclusion criteria for high-risk AML were as follows: (a) Age ≥ 60 years; (b) Prior history of MDS or myeloproliferative neoplasm (MPN); (c) Therapy-related AML or secondary AML; (d) White blood cell count $\geq 100 \times 10^9/L$; (e) Central nervous system leukemia involvement; (f) Cytogenetic or molecular genetic classification into the poor-risk category, or presence of poor-prognosis gene mutations (e.g., *TP53*, *RUNX1*, *ASXL1*, *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*, *FLT3*-ITD with high-frequency allele ratio); (g) Failure to achieve complete remission after two cycles of standard induction chemotherapy; (h) Diagnosis of refractory or relapsed AML; (i) Positive MRD prior to transplantation. High-risk MDS was defined as a score ≥ 3 according to the World Health Organization Prognostic Scoring System (WPSS) or a score > 4.5 according to the Revised International Prognostic Scoring System (IPSS-R).

Exclusion criteria were as follows: (a) severe concurrent infections; (b) severe GVHD; (c) disease relapse prior to the initiation of maintenance therapy; (d) any other condition deemed to make the patient unsuitable for maintenance therapy.

Prior to enrollment, written informed consent was acquired from all patients in compliance with the Declaration of Helsinki. Ethical approval for this study was granted by the Tianjin First Central Hospital Medical Ethics Committee, and the trial was registered at the Chinese Clinical Trial Registry (www.chictr.org; ChiCTR1900025374, 25th August 2019, retrospectively registered).

Treatment plan

All patients included in this study underwent maintenance therapy combining CHI and VEN. The treatment schedule involved CHI at 5 mg/day from days 1 to 7 or days 1 to 14 (depending on white blood cell and platelet counts), along with VEN administered as a 100 mg dose on day 1, followed by 200 mg/day from days 2 to 7 or days 2 to 14 (also adjusted based on white blood cell and platelet levels), in combination with triazole antifungals. Maintenance therapy was generally initiated around 100 days after allo-HSCT in high-risk AML/MDS patients. Treatment cycles were repeated at 2-month intervals until disease progression or unacceptable toxicity occurred. During treatment, patients were monitored for complete blood count, hepatic and renal function, drug concentrations, and other relevant indicators. Dosage adjustments were made based on laboratory results and patient tolerance. Treatment was promptly interrupted or discontinued in cases of intolerable adverse reactions. The patient enrollment flowchart and treatment schedule are summarized in Fig. 1.

Efficacy and safety assessments

Efficacy evaluations during maintenance therapy were conducted before each treatment cycle and included the following assessments from the previous cycle: peripheral blood and bone marrow smears, immunophenotyping, gene mutations or fusion gene analysis, bone marrow chimerism (STR), and lumbar puncture. Long-term survival endpoints assessed were Overall Survival (OS), Event-Free Survival (EFS), Cumulative Incidence of Relapse (CIR), and Non-Relapse Mortality (NRM). OS was defined as the time from the first dose of maintenance therapy to death from any cause or the last follow-up. DFS was defined as the duration from the initiation of maintenance therapy until the occurrence of MRD positivity or patient death. CIR represented the proportion of patients who experienced relapse or disease progression during the maintenance therapy period. NRM referred to the proportion of patients who died without prior relapse or disease progression during maintenance therapy.

In this study, all adverse events were graded and standardized in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, published by the U.S. Department of Health and Human Services in 2017. All observed symptoms and signs of adverse reactions were meticulously assessed using this framework and documented according to its defined severity grades.

These encompassed, but were not limited to, diarrhea, fatigue, rash, hematologic toxicity, hepatic insufficiency, renal insufficiency, cardiac insufficiency, and electrolyte disturbances. Additionally, the study evaluated the effect of maintenance therapy on the incidence of GVHD, as well as the rates of dose reduction, treatment delay, and therapy discontinuation attributable to the adverse reactions described above.

Data collection

Patient demographic information was collected through the digital medical record management system at Tianjin First Central Hospital. This included, but was not limited to, gender, age, present illness history, past medical history (such as chronic conditions like hypertension, diabetes, and hyperlipidemia), and physical examination records. Laboratory test results—including complete blood count, biochemical indicators such as lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), blood urea nitrogen (BUN), and bone marrow cytology—were obtained via the blood test reporting software. Imaging results were retrieved by reviewing the hospital's imaging and graphic report information system to assess disease progression and the status of tissues and organs. These included abdominal CT scans and their corresponding reports, color Doppler ultrasounds of the liver and spleen, cranial CT or MRI imaging, as well as detailed reports on bone marrow pathology and other related examinations. Follow-up survival data were obtained by reviewing patient medical records and/or conducting telephone interviews. The follow-up period concluded on March 1, 2025.

Statistical analysis

In this study, data collection and initial management of raw data were performed using Microsoft Excel. Efficacy endpoints were assessed using Kaplan–Meier analysis, which provided estimates of survival rates at different time points, median survival time along with its 95% confidence interval, and corresponding survival curves. Continuous variables were summarized using descriptive statistics—including mean, standard deviation, median, and range (i.e., minimum and maximum values)—to characterize their distributions. Categorical data were presented as frequencies and percentages. To explore the relationships among study variables, COX regression analysis was conducted using SPSS software, and hazard ratios were estimated. Statistical significance was defined as follows: a P-value ≥ 0.05 indicated no statistically significant difference between groups; a P-value < 0.05 was considered statistically significant; and a P-value < 0.01 was deemed highly statistically significant.

Results

Cohort characteristics

A total of 18 patients had been enrolled in this study. Clinical data were collected to analyze baseline characteristics. The cohort consisted of 9 male and 9 female patients, with a median age of 40 years

(range: 17–62 years). By disease classification, one patient was diagnosed with high-risk MDS, one had progressed from MDS to AML, and the remaining 16 had de novo AML. All patients were classified as having high-risk AML/MDS. Regarding high-risk features, there were 2 patients older than 60 years, 14 had r/rAML, 11 exhibited complex karyotypes, and 16 carried poor-prognosis gene mutations at initial diagnosis. Prior to transplantation, 2 patients were in partial remission (PR), and 13 were in complete remission (CR). Among the 18 patients, 11 had achieved CR with MRD negativity, while 7 patients were MRD-positive. All patients received peripheral blood-derived CD34⁺ stem cells as the graft source (5 from HLA-matched siblings, 12 from haploidentical donors, and 1 from an unrelated donor). Anti-thymocyte globulin was administered for T-cell depletion prior to HSCT. The median number of infused CD34⁺ stem cells was $4.79 \times 10^6/\text{kg}$ (range: $2.25\text{--}9.60 \times 10^6/\text{kg}$). The median time to neutrophil engraftment was 12 days (range: 10–15 days), and to platelet engraftment was 17 days (range: 14–23 days). See Table 1 for details.

Table 1
Cohort characteristics

Cohort characteristics	N = 18
Age [years, M (range)]	40(17–62)
Gender	
Male (n,%)	9(50.0)
Female (n,%)	9(50.0)
Disease type	
AML (n,%)	16(88.9)
MDS transformed to AML (n,%)	1(5.6)
MDS (n,%)	1(5.6)
Disease status at transplant	
PR(n,%)	2(11.1)
CR(n,%)	13(72.2)
MRD-(n,%)	11(61.1)
MRD+(n,%)	7(38.9)
High-risk factors	
Refractory/relapsed (n,%)	14(77.8)
> 60 y old (n,%)	2(11.1)
Complex cytogenetic aberrations (n,%)	11(61.1)
poor-prognosis gene mutations at initial diagnosis(n,,%)	16(88.9)
WBC > 100x10 ⁹ /L at diagnosis (n,,%)	2(11.1)
WPSS points ≥ 3 or IPSS-R points > 4.5(n,%)	1(5.6)
Median CD34 ⁺ cells at transplant [×10 ⁶ , M (range)]	4.79(2.25–9.60)
Donor type	
Matched sibling donor (n,%)	5(27.8)
Haplo HLA-matched donor (n,%)	12(66.7)
Unrelated donor(n,%)	1(5.6)
Median days of neutrophils ≥ 0.5 × 10 ⁹ /L	12(10–15)

Cohort characteristics	N = 18
after transplant [days, median (range)]	
Median days of platelets $\geq 20 \times 10^9/L$	17(14–23)
after transplant [days, median (range)]	
Median follow-up time [days, range]	708(136–1254)

Clinical outcomes

All 18 subjects included in the study were scheduled to begin maintenance therapy with CHI in combination with VEN at approximately 100 days post-transplantation. Patients received a median of 4 treatment cycles (range, 1–10). While all 18 patients received at least one cycle, only one patient received 10 cycles. Figure 2 summarizes the use of post-transplant CHI plus VEN as maintenance therapy and the outcomes among the 18 patients. As of March 2025, 10 patients remained in CR, 5 had experienced relapse, and 3 had died. Only one death was attributed to relapse of the primary disease; the other two deaths were due to severe infection and multiple organ failure.

Patient 2 maintained CR of the primary disease, MRD negativity, and high bone marrow chimerism throughout 3 cycles of maintenance therapy. Nevertheless, the patient died of respiratory failure resulting from a fatal episode of severe bacterial pneumonia. In the case of patient 10, 3 cycles of maintenance therapy was discontinued 200 days after transplantation. Subsequent follow-up assessments revealed recurrence of the *MLL/AF10* mutant gene. The patient was reinitiated on the fourth cycle of maintenance therapy; however, disease relapse occurred on day 289 post-transplantation. Salvage treatment with CLL1 CAR-T cell therapy was administered, and at the last follow-up, the patient remained in remission. For patient 18, bone marrow examination on day 102 post-transplantation indicated MRD-negative CR, though bone marrow chimerism was only 89.94%. The first cycle of maintenance therapy was administered as scheduled. However, before the second cycle begin, relapse of the primary disease was detected. The patient presented with a high tumor burden, suggesting a very poor prognosis. Salvage therapy involving infusion of donor CD34⁺ stem cells was performed. Unfortunately, the patient died due to disease relapse on day 157 post-transplantation.

The actual median follow-up time was 708 days post-transplantation (range, 136–1254 days). Among the high-risk AML/MDS patients in this study who received post-transplant maintenance therapy with CHI combined with VEN, the 3-year OS and DFS rates were 68.6% and 48.8%, respectively (Fig. 3A and 3B). The 3-year CIR was 44.1%, and the 3-year NRM rate was 23.6% (Fig. 3C and 3D).

Drug-related adverse reactions

The common adverse reactions associated with CHI primarily include thrombocytopenia, neutropenia, anemia, gastrointestinal reactions (such as vomiting and diarrhea), and impaired hepatic and renal

function. In this study, we systematically documented and assessed the occurrence of adverse events following each planned cycle of maintenance therapy. Results showed that hematological toxicities were the most frequently observed, aligning with previous reports on the principal toxicities of CHI. Among the 18 patients undergoing maintenance therapy, the main hematological adverse events included neutropenia (13 cases), anemia (7 cases), and thrombocytopenia (7 cases) (Table 2). Additionally, several non-hematological adverse reactions were recorded, such as fatigue (6 cases), diarrhea (11 cases), and neutropenia-associated fever (5 cases), as summarized in Table 2. Most of these adverse reactions were effectively managed with timely interventions, including antipyretics, antiemetics, antidiarrheals, and hepatorenal protective agents, indicating that patients generally tolerated CHI well. During maintenance therapy, two patients experienced extended treatment intervals because of persistent pancytopenia. No cardiac, pulmonary, renal, or neurological toxicities were observed in this study, and no treatment-related deaths occurred, and no instances of tumor lysis syndrome (TLS) were reported among the patients.

Table 2
Adverse events during maintenance therapy with chidamide plus venetoclax

Adverse effect	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	6	3	2	0
Fatigue	3	2	1	0
Hepatic insufficiency	2	1	0	0
Renal insufficiency	2	1	0	0
Cardiac insufficiency	1	1	0	0
Electrolyte imbalance	7	2	0	0
Cytopenia	14	10	3	0
Anemia	4	3	0	0
Thrombocytopenia	4	2	1	0
Neutropenia	6	5	2	0
Febrile neutropenia	3	2	0	0

GVHD

For GVHD prophylaxis, cyclosporine A, methotrexate, and mycophenolate mofetil were administered. For the treatment of GVHD, most patients received a combination of cyclosporine A and oral corticosteroids, with doses of both agents adjusted according to the individual’s clinical status. In some cases, tacrolimus was used as an alternative to cyclosporine A. Given the current lack of studies on the CHI + VEN regimen in the context of GVHD, we also documented the incidence of GVHD following the initiation

of this maintenance therapy. During the course of maintenance therapy, a total of 8 patients developed acute GVHD (aGVHD) with grade II and III being the most common (Table 3). All cases were alleviated following anti-rejection therapy, and no grade III–IV aGVHD occurred (Table 3). These findings suggest that the use of CHI combined with VEN for post-transplant relapse prevention did not lead to severe GVHD.

Table 3
New-onset GVHD during maintenance therapy with chidamide plus venetoclax

GVHD	Grade 2	Grade 3	Grade 4	Grade 5
Total	5	3	0	0
Skin	2	2	0	0
Gastrointestinal tract	2	1	0	0
Liver	1	0	0	0

Infection complications

In this study, a total of 3 patients died, with infection being the cause of death in 2 cases. During the maintenance treatment period, 5 patients developed at least one bacterial infection, and 1 patient had a fungal infection (mucormycosis), with incidence rates of 28% and 5%, respectively. There were 6 cases of CMV viremia, including 2 patients with a history of CMV infection prior to maintenance therapy and 1 who developed CMV pneumonitis, along with 1 case of EBV viremia, yielding incidence rates of 33% for CMV and 5% for EBV infection, respectively. All patients with CMV or EBV viremia received following antiviral therapy or lymphocyte depleting therapy, and viruses turned negative finally. One patient contracted COVID-19 and recovered after antiviral treatment.

Discussion

Disease relapse remains the primary factor impairing survival outcomes in high-risk AML/MDS patients after HSCT. It not only leads to low re-remission rates but also diminishes long-term survival, contributing to poor prognoses[21–25]. To address this challenge, numerous studies have proposed maintenance therapy during the post-transplant immune reconstitution phase as a strategy to prevent relapse and improve patient outcomes [3, 23, 26]. However, no consensus exists on the optimal maintenance regimen. Established approaches are increasingly limited by drug resistance and treatment failure, while novel agents remain inadequately studied in terms of dosing, timing, and toxicity profiles[3, 23, 26]. In this study, we introduced a novel maintenance therapy combining CHI and VEN in 18 high-risk AML/MDS patients. Preliminary results suggest that this regimen did not induce severe toxicities or significantly increase the incidence of graft-versus-host disease (GVHD). Furthermore, it was associated with reduced rates of relapse and sustained long-term remission.

The Ven-HMAs combination is currently approved for newly diagnosed AML patients ineligible for intensive chemotherapy and is increasingly being explored across various stages of AML treatment[23, 24]. In recent years, this combination has attracted growing interest as a maintenance therapy for high-risk AML/MDS patients following allo-HSCT, owing to its dual mechanism of synergistically inhibiting the anti-apoptotic protein BCL-2 and reversing DNA hypermethylation[8, 26, 27]. Over the past three years, our center has pioneered the use of the BCL-2 inhibitor VEN combined with hypomethylating agents (decitabine or azacitidine) as maintenance therapy to prevent relapse in high-risk AML/MDS patients after allo-HSCT, yielding benefits for the majority of transplant recipients[28].

Despite these advances, clinical experience has revealed that some patients undergoing Ven-HMAs maintenance still experience disease progression or develop resistant relapse, accompanied by short median survival and high mortality[9, 11]. Such treatment failures are often linked to high-risk genetic features, including TP53 mutations and specific fusion genes[10–12, 29]. This is particularly evident in acute monocytic leukemia, where patients generally exhibit poor sensitivity to BCL-2 inhibitors[10–12, 29]. A retrospective analysis further indicated that monocytic AML patients with genetic abnormalities such as TP53 mutations or AML1-ETO positivity are more prone to developing resistance to VEN [30]. In response to Ven-HMAs resistance, a prior report documented that the addition of the histone deacetylase inhibitor CHI could reverse resistance and restore treatment sensitivity in three patients who had failed Ven-HMAs therapy, leading to renewed remission[31]. At our center, we have expanded upon these findings with a larger sample size, reinforcing the evidence that CHI serves as an effective salvage therapy following Ven-HMAs failure (data not shown). Moreover, a prospective study (n = 48) presented at the 2024 American Society of Hematology meeting showed that the CVA regimen (CHI + VEN + azacitidine) significantly improved the complete remission rate compared to the VA regimen (VEN + azacitidine) in newly diagnosed AML patients unsuitable for intensive chemotherapy, despite an increase in grade III hematological toxicity[32].

Building on this foundation, we have proposed a combined CHI and VEN strategy and demonstrated its potential as a novel maintenance therapy to prevent relapse in high-risk AML/MDS patients post-transplantation. The CHI-VEN combination represents a multidimensional innovation in overcoming BCL-2 inhibitor resistance and improving treatment outcomes for AML[33]. As an oral histone deacetylase inhibitor, CHI enhances VEN-induced apoptosis through epigenetic remodeling[34, 35]. This regimen acts synergistically to overcome drug resistance through multiple mechanisms, including: (1) co-targeting key signaling pathways such as PI3K/AKT and JAK2/STAT3, thereby cooperatively promoting apoptosis in AML cell lines and primary cells[14, 19]; (2) promoting DNA double-strand breaks and modulating the balance between anti-apoptotic and pro-apoptotic proteins—for instance, downregulating MCL-1 and Bcl-xL while upregulating Bim—thus synergizing with VEN to exert anti-AML effects[20]; and (3) inhibiting the expression of key glycolytic enzymes, leading to energy depletion in AML cells and further enhancing treatment efficacy[19, 35].

Conclusion

The combination of CHI and VEN represents an innovative strategy to overcome drug resistance in high-risk AML/MDS through epigenetic and metabolic mechanisms. As post-transplant maintenance therapy, it has shown promising improvements in overall survival and relapse reduction, without significantly increasing toxicity compared with historical controls. Future studies with larger sample sizes and extended follow-up are warranted to confirm its long-term efficacy and safety.

Declarations

Ethics statement

This study was conducted in compliance with the guidelines of the Ethics Committee for New Technology/New Treatment Projects at Tianjin First Center Hospital. Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki. The study protocol received formal approval from the aforementioned Ethics Committee.

Competing Interests

The authors declare no competing interests.

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Conflict of interest

The authors declare no conflicts of interest related to this work.

Author contributions

MFZ designed the research. YDP and XSL analyzed the data. CCL and HTM wrote the manuscript. HRL and XX revised the manuscript. All authors approved the final version of the manuscript.

Date available statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figures

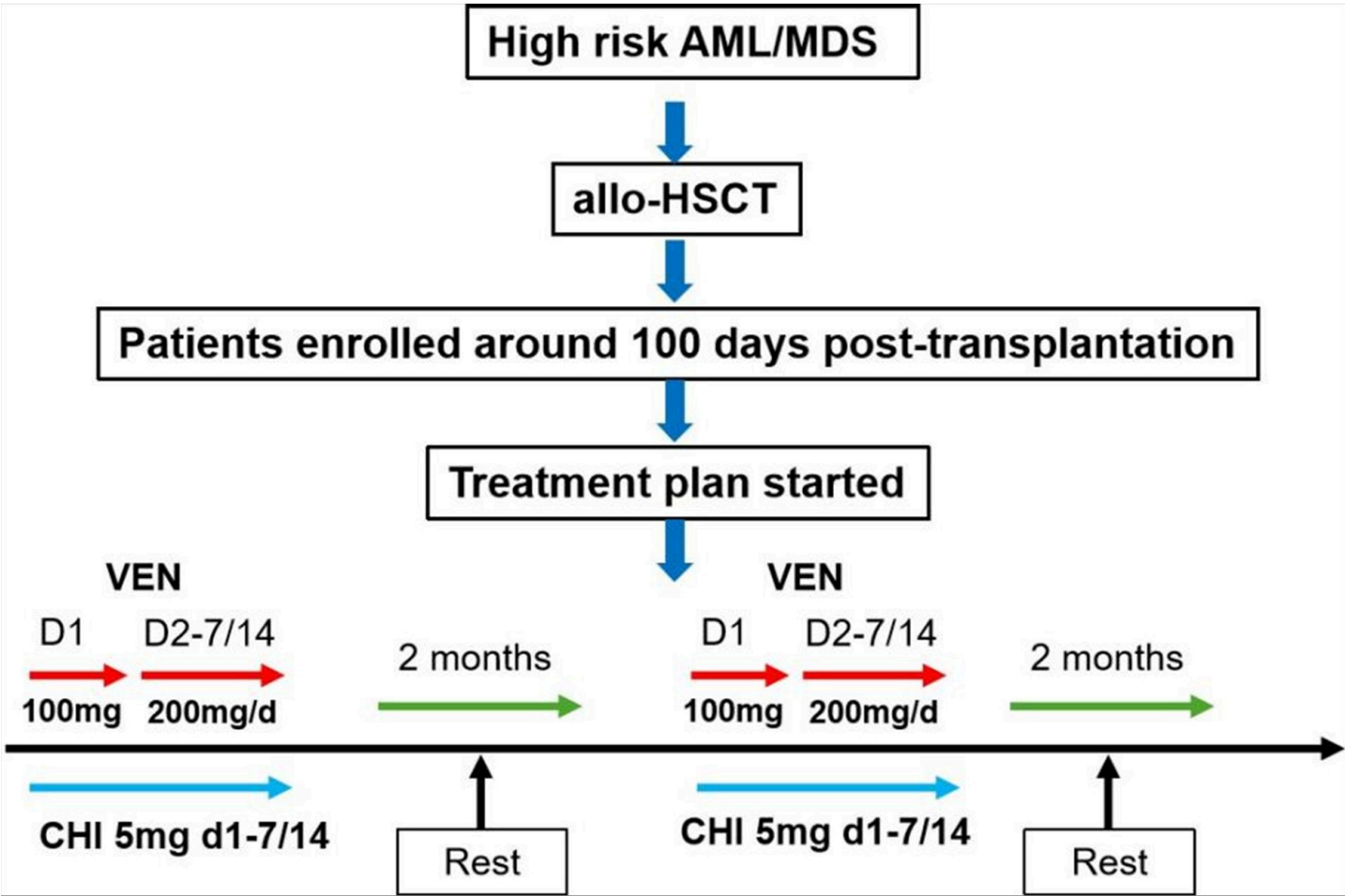


Figure 1

Patient enrollment flow chart and treatment plan

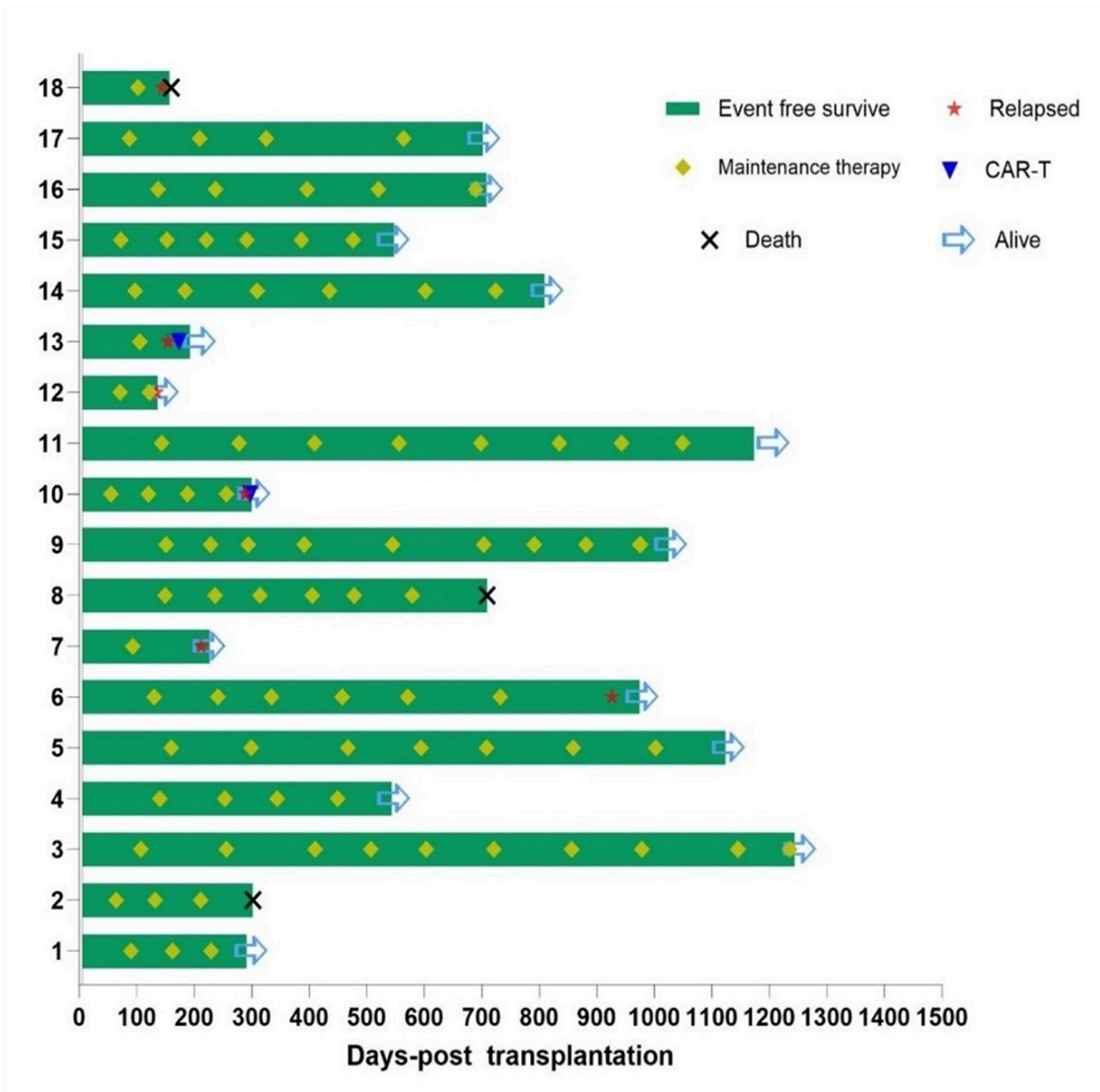


Figure 2

Clinical outcome of maintenance therapy after transplantation for 18 enrolled patients

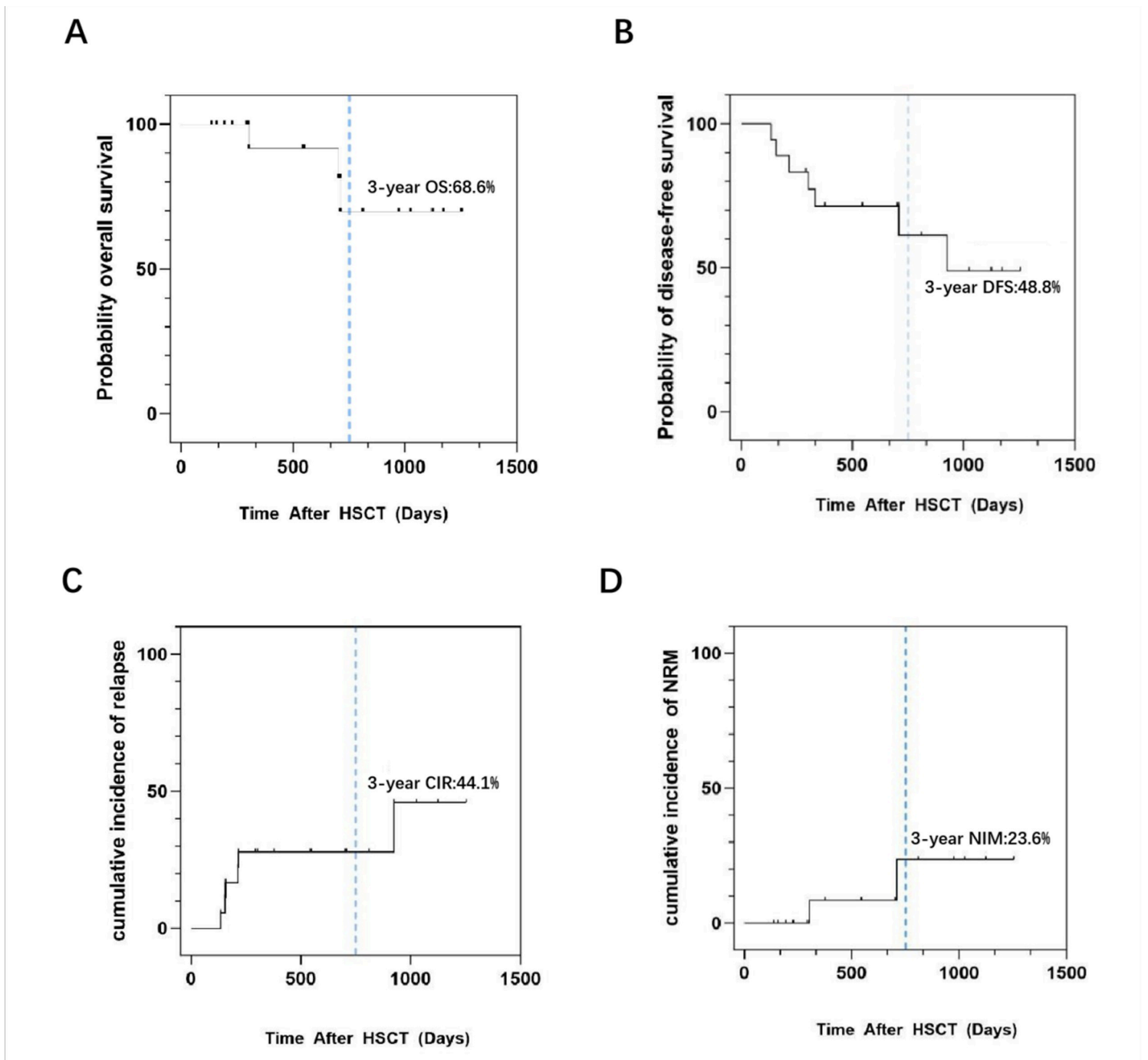


Figure 3

A and B. 3-Year overall survival and disease-free survival; **C and D.** 3-Year cumulative incidence of relapse and nonrelapse mortality