

Successful treatment of two relapsed patients with t(11;19)(q23;p13) acute myeloid leukemia by CLAE chemotherapy sequential with allogeneic hematopoietic stem cell transplantation: Case reports

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Abstract. The prognosis of patients with relapsed/refractory acute myeloid leukemia (R/R AML) is poor, with a 3-year overall survival rate of 10%. Patients with translocation (t(11;19)(q23;p13)) have a higher risk of relapse and there is no optimal regimen for these patients. The present study treated two young patients with t(11;19)(q23;p13) AML, who relapsed after one or two cycles of consolidation, with a salvage treatment consisting of sequential cladribine, cytarabine and etoposide (CLAE) and allogeneic hematopoietic stem cell transplantation (allo-HSCT). Both neutrophil and platelet engraftments were achieved within 15 days, and no severe transplant-related complications and graft-versus-host diseases were observed. Following allo-HSCT, both patients achieved complete hematologic and cytogenetic remission. Decitabine was used for the prophylaxis of relapse. The two patients remained alive and disease-free for 100 days following allo-HSCT. The results presented here suggest that CLAE regimen sequential with allo-HSCT may be effective in treating patients with R/R AML, with t(11;19)(q23;p13). However, further studies and a larger sample size are required to validate the effectiveness of this treatment regimen.

Introduction

Acute myeloid leukemia (AML) is a malignant clonal disorder that originates from hematopoietic stem cells by uncontrolled proliferation and suppressed differentiation of blast cells in the myeloid lineage, which infiltrate the bone marrow, blood and other tissues, including lymph node or spleen (1). AML is the most common type of acute leukemia in adults, which accounts for 1.3% of new cancer cases annually in the United States (2). AML can occur in any age group; however, the most affected patients are older adults, with a median age at diagnosis of 68 years (2). It is estimated that 10-40% of patients newly diagnosed with AML fail to achieve complete remission (CR) with the standard induction chemotherapy treatment, and these cases are defined as primary refractory cases (3). In addition, most patients who achieve CR will eventually relapse because of unfavorable cytogenetics at diagnosis and old age (4,5). Patients with relapsed/refractory (R/R) AML have a poor prognosis, with a 3-year overall survival (OS) rate of only 10%, thus the majority of patients die from recurrence (5,6).

Currently, there is no standard treatment regimen for patients with R/R AML, except for allogeneic hematopoietic stem cell transplantation (allo-HSCT) (6,7). Most R/R AML patients are old and have less than ideal performance status or without a matched related donor, so only a minority of patients are suitable for allo-HSCT (5). Thus, it remains critical to identify early prognostic factors and select the appropriate conditioning regimens for allo-HSCT for the effective treatment of patients with AML.

Cladribine is a deoxyadenosine analogue that can be rapidly phosphorylated into a triphosphate form, which resists degradation by adenosine deaminase and increases cytotoxic levels in the intracellular space, inhibits DNA synthesis and induces cell apoptosis (8). Previous studies have demonstrated that cladribine combination regimens are effective in patients with R/R AML and may overcome abnormal chromosome karyotypes with poor prognosis (8,9). In addition, cladribine-based chemotherapy regimens sequential with allo-HSCT are considered promising treatment strategies for patients with R/R AML (10,11).

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Abbreviations: R/R AML, relapsed/refractory acute myeloid leukemia; CLAE, cladribine, cytarabine and etoposide; allo-HSCT, allogeneic hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CR, complete remission; MRD, minimal residual disease; OS, overall survival

Key words: CLAE, relapse, acute myeloid leukemia, translocation (11;19) (q23;p13), allogeneic hematopoietic stem cell transplantation

Conventional cytogenetic data has established prognostic indications for patients with AML (2). Based on karyotypic analysis, recurring translocations (t) or inversions (inv) or deletion (del), including t(6;9), t(v.11q23.3), t(9;22), inv(3), t(3;3), -5, del(5q), -7 and -17 are associated with adverse risk of AML, designated by the World Health Organization (2). t(11;19)(q23;p13) is a rare recurrent cytogenetic abnormality in patients with AML; however, its clinical and genetic characteristics are not yet fully understood (12). Previous studies have reported that the prognosis of patients with AML, with t(11;19)(q23;p13) is poor, with a median OS time <1 year (13,14). It has been reported that CLAM (cladribine, cytarabine, mitoxantrone) and MEC (mitoxantrone, etoposide, and cytarabine) chemotherapy regimens exhibit promising activity in patients with R/R AML (15,16), thus, CLAM was selected as the regimen in the present study. The present study reported two relapsed patients with t(11;19)(q23;p13) AML who were successfully treated with cladribine, cytarabine and etoposide (CLAE) chemotherapy sequential with allo-HSCT.

Case reports

The present study was approved by the Institutional Review Board of The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (Huai'an, China; approval no. YX-P-2020-004-01) and performed in accordance with the Declaration of Helsinki (17). Written informed consent was provided by both patients prior to the study start.

Case 1. On December 26, 2018, a 23-year-old man was admitted to The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University due to stomachaches and experiencing weakness. Peripheral blood analysis revealed the following: White blood cell count of $70.85 \times 10^9/l$, hemoglobin level of 114 g/l and a platelet count of $26 \times 10^9/l$. In addition, the bone marrow (BM) smear revealed 42% of blast cells. Immunophenotype analysis indicated that 33% of the blast cells were abnormal, and demonstrated positive labeling for myeloperoxidase (MPO), cluster of differentiation (CD)13, CD33, CD34, CD38 and CD117. The karyotype was 46,XY,t(11;19)(q23;p13)[17]/46,XY[3] (Fig. 1). Aberrant *EVII* and *NRAS* expression levels were detected (mutation frequency, 8.32%) via reverse transcription (RT)-PCR and sanger sequencing analyses, while fusion genes were detected via RT-PCR analysis. Total RNA was extracted using the Omega whole-blood RNA extraction kit (cat. no. R6616-02; Omega Bio-Tek, Inc.), according to the manufacturer's protocol. Nested RT-PCR analysis was performed, and the reaction system was used as previously described (18,19). AML-associated mutated genes were detected using high-throughput sequencing technology. Total DNA was extracted using the whole blood DNA extraction kit (cat. no. D3392-02; Omega Bio-Tek, Inc.), and genetic mutations were detected by the Kindstar Global Medical Laboratory Center (<http://www.kindstar.com.cn/kindstar/cn/platform.html>), using sanger sequencing as previously described (19,20). Notably, *MLL* rearrangement was not detected. The patient was diagnosed with AML (M4) according to the FAB (French American British) classification system (21). The patient was treated with standard '3+7' regimen with idarubicin and cytarabine (IA) as induction

therapy and achieved CR, with 1.5% blasts after one cycle. The minimal residual disease (MRD) detection via flow cytometric (FCM) analysis was negative (<0.01%) and was followed by three cycles of consolidation (intermediate dose cytarabine with $2.0 \text{ g/m}^2 \times 6$ times). Following the third consolidation chemotherapy, MRD detection was positive, with 6% abnormal cells expressing CD13, CD33 and CD34 via FCM analysis, and the BM smear indicated relapse (8.5% of blast cells; Fig. 2). The patient received one cycle of homoharringtonine, daunorubicin and cytarabine reinduction chemotherapy regimen; however, he failed to achieve CR. The BM blasts were 11.5% and the MRD was 10.5%. The patient subsequently received intense CLAE chemotherapy (cladribine $5 \text{ mg/m}^2/\text{dx}5\text{d}$, cytarabine $1.5 \text{ g/m}^2/\text{dx}5\text{d}$ and etoposide $100 \text{ mg/m}^2/\text{dx}3\text{d}$), and underwent haploid allo-HSCT (stem cells from his father) 3 days after CLAE chemotherapy, with the conditioning regimen of Flu-Bu-ATG (fludarabine $30 \text{ mg/m}^2/\text{dx}5\text{d}$, busulfan $3.2 \text{ mg/kg}/\text{dx}3\text{d}$ and ATG $2.5 \text{ mg/kg}/\text{dx}4\text{d}$). Graft-versus-host diseases (GVHDs) were prevented by cyclosporin A, methotrexate and mycophenolate mofetil (Fig. 3). A total of $12.5 \times 10^8/\text{kg}$ mononuclear cells and $2.75 \times 10^6/\text{kg}$ CD34⁺ cells from the donor were intravenously injected into the patient, and no serious complications occurred during allo-HSCT. The neutrophil and platelet engraftments were achieved on days 14 and 12, respectively (Fig. 4C and D). The MRD was 10^{-4} as detected via FCM analysis, and the chromosome changed to normal karyotype 1 month after transplantation. The donor chimerism rate was 100% following multiplex PCR analysis of short tandem repeats at +14 days, +30 days and +60 days after transplantation. The decitabine regimen (decitabine $15 \text{ mg/m}^2/\text{dx}5\text{d}$) was implemented every 3 months for the prophylaxis of relapse, beginning at 2 months after allo-HSCT. The patient received follow-up in the clinic weekly and remained in a disease-free survival state based on the last follow-up at 4.3 months after allo-HSCT.

Case 2. On May 12, 2019, a 31-year-old man was admitted to The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University due to fever and bleeding gums. Peripheral blood analysis revealed the following: White blood cell count of $10.37 \times 10^9/l$, hemoglobin level of 114 g/l and a platelet count of $8 \times 10^9/l$. In addition, the BM smear revealed 28% of blasts cells. FCM analysis exhibited 39% of blast cells, and demonstrated positive labeling for MPO, CD13, CD15, CD33, CD38, CD56 and human leukocyte antigen-DR (HLA-DR). The karyotype was 46,XY,t(11;19)(q23;p13.1)[18]/46,XY[2] (Fig. 1). Aberrant *EVII* and *MLL/ELL* rearrangement were detected using the same methods performed for patient 1. The patient was diagnosed with AML (M2) according to the FAB classification and was subsequently treated with two cycles of IA regimen as induction, and achieved CR with 2.0% blasts. The MRD was negative (<0.01%) and was followed by one cycle of consolidation with an intermediate dose of cytarabine with $2.0 \text{ g/m}^2 \times 6$ times. The patient was re-admitted due to severe crissum infection on October 10, 2019. The BM smear revealed 58% of blast cells 6 months after consolidation, suggesting disease relapse (Fig. 2). The patient underwent matched unrelated allo-HSCT (stem cells from a donor at the Chinese bone marrow bank)

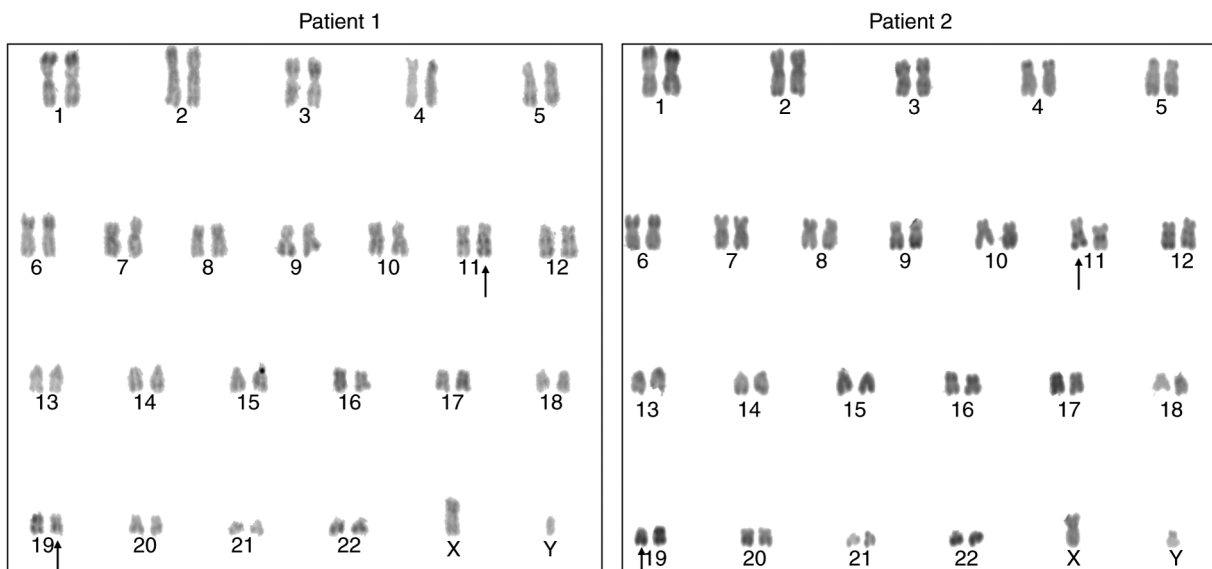


Figure 1. Chromosome karyotype of two t(11;19) patients with AML. G-banded karyotype of BM cells at the newly diagnosed stage. Patient 1: Representative images of the karyotype of BM cells with t(11;19)(q23;p13). Patient 2: Representative images of the karyotype of BM cells with t(11;19)(q23;p13.1). The arrows indicate translocated chromosomes. t, translocation; AML, acute myeloid leukemia; BM, bone marrow.

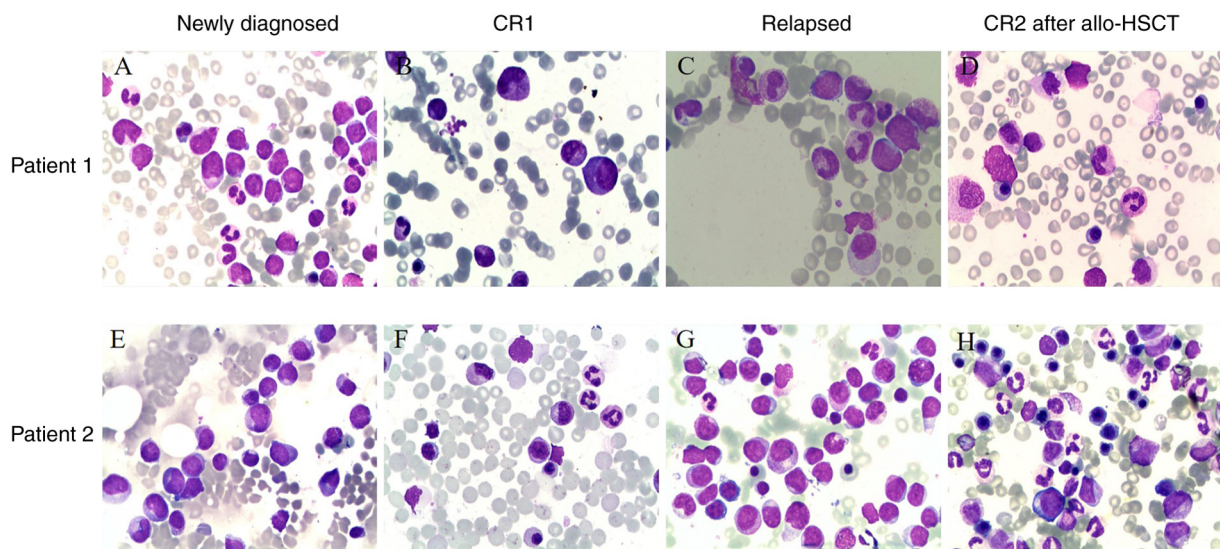


Figure 2. Morphological features of two patients with AML at different stages of the disease. May-Grüwald-Giemsa-stained BM smear (magnification, x1,000). Patient 1: (A) Morphological features of BM at the newly diagnosed stage, granulocytes increased and myeloblasts accounted for 42%. The positive rate of myeloperoxidase staining was 76%. (B) Morphological features following induction chemotherapy. (C) Morphological features at the relapsed stage, myeloblasts accounted for 9%. (D) Morphological features following allo-HSCT. Patient 2: (E) Morphological features of BM at the newly diagnosed stage, granulocytes increased and myeloblasts accounted for 28%. The positive rate of myeloperoxidase staining was 92%. (F) Morphological features following induction chemotherapy. (G) Morphological features at the relapsed stage, myeloblasts accounted for 58%. (H) Morphological features following allo-HSCT. AML, acute myeloid leukemia; BM, bone marrow; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission.

and simultaneously received antibiotics to control the crissum infection. The patient received intense CLAE chemotherapy (cladribine 5 mg/m²/dx5d, cytarabine 1.5 g/m²/dx5d and etoposide 100 mg/m²/dx3d) and conditioning regimen, followed by allo-HSCT. The BM smear revealed 23% of blasts cells following CLAE, thus the total dose of busulfan in the conditioning regimen was adjusted to 3.2 mg/kg/dx4d. The conditioning regimen consisted of the following: Fludarabine 30 mg/m²/x5d, busulfan 3.2 mg/kg/dx4d and ATG 2.5 mg/kg/dx4d. Cyclosporin A, methotrexate and mycophenolate mofetil were used to prevent GVHDs. A total of

8.0x10⁸/kg mononuclear cells and 6.72x10⁶/kg CD34⁺ cells were intravenously infused into the patient. The patient suffered crissum abscess and sepsis during transplantation. The neutrophil and platelet engraftments were achieved on days 12 and 14, respectively (Fig. 4C and D). MRD detection was negative (<10⁻⁴), and the chromosome changed to normal karyotype 1 month after transplantation. The donor chimerism rate was 100% at +14 days, +30 days and +60 days following transplantation. The decitabine regimen was implemented for the prophylaxis of relapse. The patient received follow-up in the clinic weekly and achieved CR based on the last follow-up

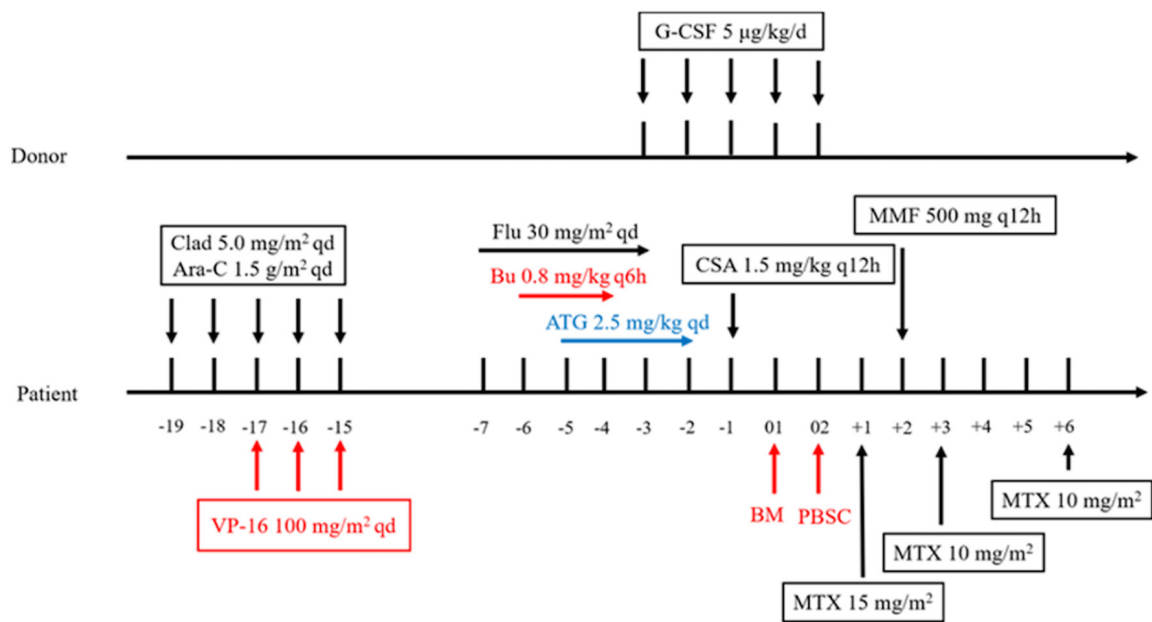


Figure 3. Flowchart of regimen consisting of cladribine, cytarabine and etoposide chemotherapy, and allogeneic hematopoietic stem cell transplantation. Clad, cladribine; Ara-C, cytarabine; VP-16, etoposide; Flu, fludarabine; Bu, busulfan; ATG, anti-thymocyte globulin; G-CSF, granulocyte colony-stimulating factor; CSA, cyclosporin A; BM, bone marrow; PBSC, peripheral blood stem cell; MTX, methotrexate; MMF, mycophenolate mofetil.

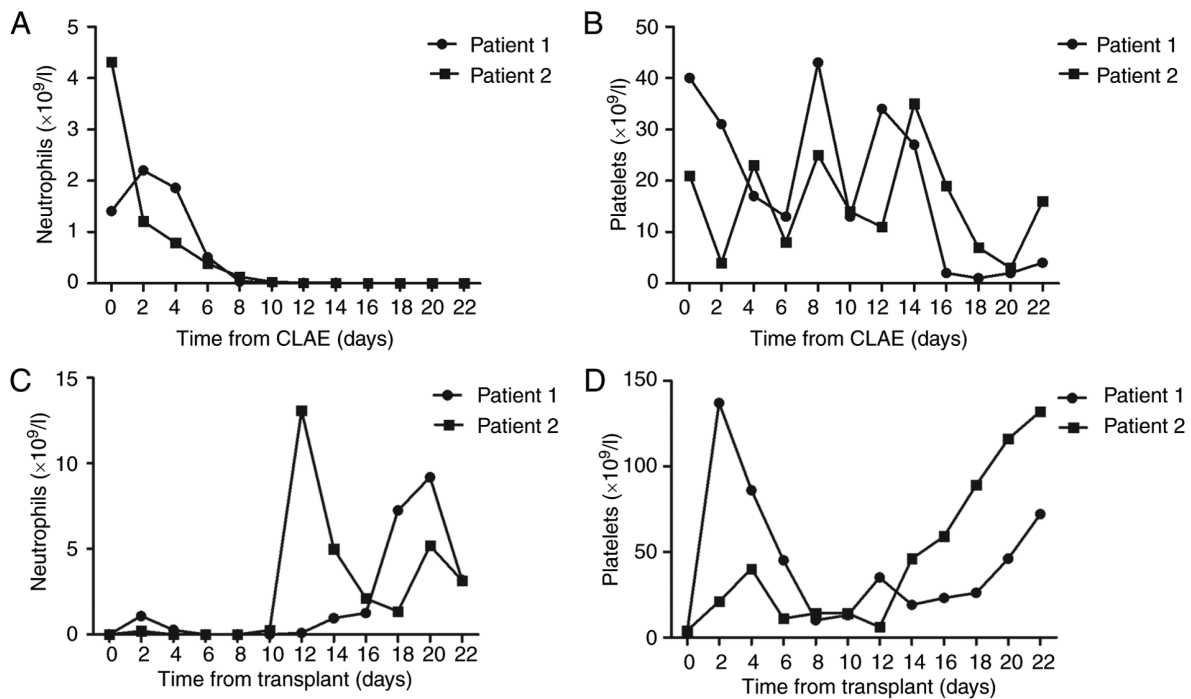


Figure 4. Recovery of platelets and neutrophils following allo-HSCT. (A and B) The recovery times achieved a normal neutrophil count following CLAE regimen of patient 1 and patient 2. (C and D) The recovery times achieved a normal neutrophil count following allo-HSCT of patient 1 and patient 2. allo-HSCT, allogeneic hematopoietic stem cell transplantation; CLAE, regimen consisting of cladribine, cytarabine and etoposide.

at 3.5 months after allo-HSCT. The characteristics of both patients are presented in Table I.

Discussion

In the present study, two relapsed patients with t(11;19)(q23;p13) AML were successfully treated with CLAE regimens sequential with allo-HSCT. Both patients achieved CR.

The intense chemotherapy prior to allo-HSCT decreased the leukemia burden and inhibited the immune system of the recipient to promote the implantation of HSCs. The results presented here confirm the efficacy of intense CLAE chemotherapy sequential with allo-HSCT in young relapsed patients with t(11;19)(q23;p13) AML. Hematological toxicity and other side effects, including hemocytopenia, nausea and vomiting, infection were presented during treatment.

Table I. Patient characteristics.

Characteristic	Case 1	Case 2
Age, year	23	31
Sex	Male	Male
WBC, $\times 10^9/l$	70.85	10.37
PLT, $\times 10^9/l$	26	8
Blasts in bone marrow, %	42	39
FAB	AML-M4	AML-M2
Cytogenetics	46,XY,t(11;19)(q23;p13)[17]/46,XY[3]	46,XY,t(11;19)(q23;p13.1)[18]/46,XY[2]
Molecular biology	EVI1, NRAS	EVI1, MLL/ELL
Risk stratification	High risk	High risk
Induction chemotherapy regimen	IA	IA
MRD after induction chemotherapy	Negative	Negative
Disease status before HSCT	Relapsed	Relapsed

WBC, white blood cells; PLT, platelet; FAB, French American British; MRD, minimal residual disease, HSCT, hematopoietic stem cell transplantation, IA, idarubicin and cytarabine.

Reciprocal chromosomal translocations can cause genetic aberrations in pediatric and adult patients with AML (22,23). t(11;19)(q23;p13) is a relatively rare recurrent cytogenetic aberration that occurs in patients with AML (12). *MLL* is involved in the majority of 11q23 translocations of acute leukemias, whereby rearrangement of *MLL* results in fusion of the *MLL* gene with its partner gene (12). However, heterogeneity rearrangements have been observed at this chromosomal region (12,24). *NRAS* and *KRAS* are frequently mutated in *MLL*-rearranged leukemia (25). The present study assessed two patients with t(11;19)(q23;p13) AML, patient 1 (M4) had no *MLL* rearrangement, while patient 2 (M2) had *MLL/ELL* rearrangement, and both presented with early relapse (less than half a year). Consistent with previous findings (12-14), the results of the present study demonstrated that t(11;19)(q23;p13) was associated with a poor prognosis and short OS time in patients with AML, and indicated that it is necessary for these patients to receive allo-HSCT in first CR.

The present study is not without limitations. First, the *MLL* rearrangement in patient 2 was not detected via fluorescence *in situ* hybridization as the sample size was too small. Secondly, both patients had a relatively short follow-up period, thus further studies are required with extended follow-up periods and larger sample sizes.

Intensive chemotherapy is used to eliminate leukemia cells, followed by allo-HSCT as consolidation therapy for patients with R/R AML (26). This regimen has been demonstrated to improve the long-term survival rate from 20 to 50%; however, reinduction chemotherapy-related side effects must be acceptable to patients (27). Previous studies have reported that FLAG-IDA (granulocyte colony-stimulating factor, fludarabine, cytarabine, and idarubicin), CLAG (cladribine, cytarabine, granulocyte colony-stimulating factor), CLAM (cladribine, cytarabine, mitoxantrone) and MEC (mitoxantrone, etoposide, and cytarabine) chemotherapy regimens achieve high CR rates in patients with R/R AML (28-31). However, CR rates in response to common salvage regimens decrease (10-15%) in refractory or early relapsed patients with

AML (26). Furthermore, common conditioning regimens followed by allo-HSCT in patients with R/R AML exhibit disappointing results (32,33). Thus, the concept of chemotherapy sequential with allo-HSCT was developed (26). Recently, it has been demonstrated that high-dose melphalan-based sequential conditioning chemotherapy followed by allo-HSCT is feasible in patients with R/R AML (26). Another study reported the feasibility and efficacy of FLAG-IDA chemotherapy sequential with Flu-Bu3 conditioning regimen in patients with refractory AML (34). Based on previous studies (28-31) and patient characteristics, the present study selected the CLAE regimen sequential with Flu-Bu conditioning regimen for allo-HSCT in the assessed patients. Patient 1 received CLAE regimen sequential with haploid transplantation, and exhibited granulocyte deficiency at 21 after chemotherapy, the neutrophil and platelet engraftments were achieved on days 14 and 12. Patient 2 received CLAE regimen sequential with hematopoietic stem cell transplantation from unrelated donors, the neutrophil and platelet engraftments were achieved on days 12 and 14. No serious transplant-related complications occurred in patient 1, while patient 2 experienced crissum abscess and sepsis, which were effectively controlled with antibiotics. Any grade of GVHDs were absent in both cases. MRD was negative in both patients, and the donor chimerism rate was 100%, while the karyotype of chromosomes changed to normal karyotype. Decitabine was used to prevent disease relapse following transplantation, and both patients remained alive and disease-free based on the last follow-up.

In conclusion, the results of the present study demonstrated the high antileukemic efficacy and acceptable toxicity of CLAE regimen sequential with allo-HSCT for patients with t(11;19)(q23;p13) AML. The results presented here suggest that t(11;19)(q23;p13) is a poor prognostic factor in AML, and that the CLAE regimen sequential with allo-HSCT may be an effective treatment strategy for patients with t(11;19)(q23;p13) R/R AML. However, prospective studies with larger sample sizes are required to validate the effectiveness of this treatment regimen.

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Availability of data and materials

The data that support the findings of the present study are available from Kindstar Global Medical Laboratory Center (<https://www.kindstar.com.cn/platform.html>); however, restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission from Kindstar Global Medical Laboratory Center.

Authors' contributions

ST collected patient data and drafted the initial manuscript. CW and LY conceived and designed the present study. ST revised the manuscript along with LS, YD, YC, YG, YL, YHD, ZZ, BD and ZH, and these individuals were responsible for the treatment of the patients. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (Huai'an, China; approval no. YX-P-2020-004-01) and performed in accordance with the Declaration of Helsinki. Written informed consent was provided by both patients prior to the study start.

Patient consent for publication

Both patients provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

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