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Brief Report

A modified shortened chemotherapy for reinduction therapy in relapsed adult Ph$^-$ acute lymphoblastic leukemia

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ABSTRACT

Remission rates remain low among adult patients with relapsed Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph$^-$ ALL). The standard 4-week reduction chemotherapy regimen cannot be administered due to serious hematopoietic toxicity and infection during induction therapy, which can decrease the elimination of blast cells. In this study, a modified shortened P-CIOD chemotherapy protocol (comprising pegaspargase, cyclophosphamide, idarubicin, vindesine, and dexamethasone) was used as a reinduction therapy for relapsed Ph$^-$ ALL. Remarkably, 80% (4 out of 5) of the patients achieved complete remission (CR) with minimal residual disease (MRD) negativity and without treatment-related mortality. Two patients were lost to follow-up after consolidation treatment, while the remaining three patients survived. The longest disease-free survival (DFS) recorded was 27 months. The results suggest that the novel protocol shows a favorable second complete remission (CR2) with low toxicity for adult patients with relapsed Ph$^-$ ALL.

Keywords: modified shortened chemotherapy, reinduction therapy, adult Ph$^-$ acute lymphoblastic leukemia

INTRODUCTION

Although multi-drug chemotherapy regimens achieve 85%–90% complete remission (CR) in adult Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph$^-$ ALL) patients, most patients who attain CR eventually relapse[1–2]. This underscores the need for exploring salvage therapies for relapsed Ph$^-$ ALL, including augmented cytotoxic chemotherapy, reformulated single-agent chemotherapy, immunotherapy, and novel monoclonal antibody therapy. Immunotherapies such as chimeric antigen receptor T (CAR-T) cells and monoclonal antibodies (e.g., blinatumomab) have shown good outcomes in relapsed Ph$^-$ ALL patients[3–6]. However, these methods are mainly used for B cell ALL, and the long-term survival outcomes need to be further improved[7–11]. When applying induction therapy, negative minimal residual disease (MRD) has been reported as a strong prognostic factor associated with inferior outcomes[12]. Although the rate of end-induction MRD positivity in adult patients under pediatric-inspired protocols is higher than that in pediatric ALL patients, the results are superior to present adult protocols[13]. However, guidelines from the National Comprehensive Cancer Network (NCCN) recommend the use of clinical trials to identify novel protocols for induction therapy for

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newly diagnosed adult ALL patients. At present, outcomes are very poor among patients with relapsed Ph⁻ ALL treated with the current protocol[13]. Therefore, induction therapy requires further development to improve CR with negative MRD outcomes to enhance overall survival (OS) rates in adult patients with relapsed Ph⁻ ALL.

The standard 4-week reduction chemotherapy regimen for ALL, which usually consists of vincristine, corticosteroid, L-asparaginase, and anthracycline, is generally effective and currently the most utilized protocol. Idarubicin is a new anthracycline that is superior to daunomycin for the treatment of ALL[14]. The idarubicin-based protocol has achieved good outcomes as an induction therapy for adult relapsed or refractory (R/R) Ph⁻ ALL[15–17]. However, weekly doses of idarubicin and vincristine for 3 weeks, along with continuous 4 weeks of corticosteroids, cannot be administered because of serious hematopoietic toxicity and infection during induction therapy[18], which can decrease the elimination of blast cells. Higher doses of dexamethasone have yielded better responses in ALL patients[19]. Some reports also showed that lower blast levels at day 14 of chemotherapy indicated better survival outcomes[20]. Therefore, a novel protocol should be explored to shorten chemotherapy duration, which can allow all drugs to be effectively incorporated into reinduction chemotherapy, reduce infection risk, and lower blast cell levels on day 14, leading to earlier remission and higher MRD negativity. In this study, we administered a modified shortened chemotherapy of P-CIOD protocol (pegaspargase, cyclophosphamide, idarubicin, vindesine, and dexamethasone) (AALLXQCQC-2019 protocol) to patients with relapsed Ph⁻ ALL.

The primary objective of this study is to assess the efficacy and toxicity of the aforementioned reinduction regimen, which are represented by the CR rate and induction death rate.

SUBJECTS AND METHODS

Patients

Five adult patients with relapsed Ph⁻ ALL were enrolled in this study between 2019 and 2021. All patients experienced relapse after chemotherapy without transplantation. This study was approved by the Ethics Committee of Xinqiao Hospital of Army Medical University and was conducted according to the Good Clinical Practice (GCP) in China and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients and/or their legal guardians.

Definition

Relapse was defined as ≥5% blast cells in the blood or bone marrow (BM) by microscopic morphological examination after achieving CR following chemotherapy.

Treatment protocol

The reinduction protocol (P-CIOD) consisted of pegaspargase 2500 IU/m^2 on day 1 and day 14, cyclophosphamide 800 mg/m^2 on day 1, idarubicin 6–8 mg/m^2 (total 10 mg) on days 1–3, vindesine 2–3 mg/m^2 (total 4 mg) on day 1, and dexamethasone 20 mg/d on days 1–7.

Assessment of response and toxicities

BM examinations were performed on day 28 of the reinduction treatment. CR was defined histologically as less than 5% blast cells in the BM, and negative MRD as <0.01% BM blast cells assessed by multiparameter flow cytometry for leukemia-associated profiles[3]. CR classification also included ≥ 1-month normal maturation of all cell components in the BM, no extramedullary leukemia, and normal peripheral blood cell count. Partial remission (PR) was defined as >5% and <20% blast cells in the patients' BM.

Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CT-CAE v4.0, National Cancer Institute, Bethesda, MD, USA).

RESULTS

Patient characteristics

A total of 5 patients (3 males and 2 females) were enrolled in this study. The median age was 26 years old (range: 19–48 years). The demographic and clinical characteristics of the patients are summarized in ***Table 1***.

Outcome of reinduction treatment

An overview of the treatment and outcome for the 5 patients with relapsed adult Ph⁻ ALL is depicted in ***Fig. 1***. All patients completed the reinduction treatment without fatal complications. The second complete remission (CR2) rate was 80.0% (4 of 5 patients) with MRD negativity. One patient who achieved PR subsequently achieved remission when treated with blinatumomab, resulting in a final CR2 rate of 100.0% (5/5).

Table 1 **Patient characteristics and treatments**

No.	Gender	Age	Immuno-phenotype	Risk group at initial diagnosis	NGS and PCR mutation findings	Karyotype	No. of prior therapy	Prior therapy	MRD situation before relapse	Time of relapse after CR	Response after induction therapy	Post-induction treatment
Pt 1	Female	19	My+ B-cell	High-risk	FLT3-ITD, WT1	46, XX[7]	Not available	CCCG-ALL-2012	CR with MRD−	5 years	CR with MRD−	Allo-HSCT
Pt 2	Female	48	B-cell	High-risk	Negative	46, XX[20]	4	CVTLP EAOD + MTX P-EAOD + MTX P-EAOD + MTX	CR with MRD+	5 months	CR with MRD−	Chemotherapy
Pt 3	Female	19	B-cell	High-risk	WT1	46, XX[20]	4	VILP CAM CAM CHOP + MTX	CR with MRD−	5 months	CR with MRD−	Chemotherapy
Pt 4	Male	26	B-cell	High-risk	KRAS	46, XY, inv (9) (p12q13)c[3]	2	VTLP HyperCVAD-B	CR with MRD+	2 months	PR with 5% blasts	Chemotherapy
Pt 5	Male	34	My+ B-cell	High-risk	WT1	46, XY[5]	5	CVILP CAM + MTX HD-MTX + THP MTX + Ara-c MTX + Ara-c	CR with MRD−	1 year	CR with MRD−	Allo-HSCT

NGS: next-generation sequencing; PCR: polymerase chain reaction; MRD: minimal residual disease; CR: complete remission; Allo-HSCT: allogeneic hematopoietic stem cell transplantation; CVTLP: cyclophosphamide, vincristine or vindesine, daunorubicin, prednisone, asparaginase; P-EAOD+MTX: pegylated asparaginase, etoposide, cytarabine, vincristine, dexamethasone, methotrexate; MTX: methotrexate; VILP: vincristine or vindesine, idarubicin, prednisone, asparaginase; CAM: cyclophosphamide, cytarabine, 6-Mercaptopurine; HyperCVAD: hyper-fractionated cyclophosphamide, vincristine or vindesine, dexamethasone, doxorubicin, methotrexate, cytarabine; PR: partial remission; Ara-c: cytarabine.

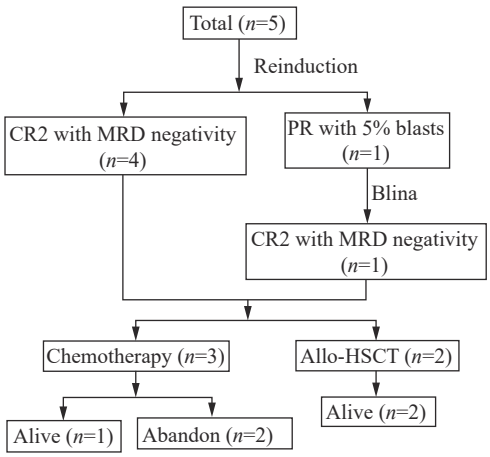

***Fig. 1* Overview of treatment and outcome regarding 5 patients with relapsed Ph⁻ ALL.** Ph⁻ ALL: Philadelphia chromosome-negative acute lymphoblastic leukemia; CR2: second complete remission; MRD: minimal residual disease; PR: partial remission; Blina: Blinatumomab; Allo-HSCT: allogeneic hematopoietic stem cell transplantation.

Toxicities

The hematological toxicities observed in this study are as follows: grade 3–4 neutropenia in 100.0%, anemia in 80.0% (4/5), and thrombocytopenia in 80.0% (4/5). Non-hematological toxicities were observed. All 5 patients developed neutropenic fever during reinduction treatment, 1 with documented bacteremia and 4 with no identifiable infection source. None of the patients died.

Outcome of post-induction treatment

Of the 5 patients, 2 underwent subsequent allogeneic hematopoietic stem cell transplantation (allo-HSCT) after achieving CR and remained in remission, and the other 3 patients continued consolidation and maintenance treatment with chemotherapy. Among the 3 patients with consolidation and maintenance chemotherapy, 1 remained in remission and 2 did not return to the hospital after consolidation treatment. The longest disease-free survival (DFS) time among the 3 patients who attended follow-up was 27 months.

DISCUSSION

The rate of remission was notably low among the adult patients with relapsed Ph⁻ ALL. Here, we evaluated the efficacy and safety of a novel reinduction chemotherapy protocol for adult patients with relapsed adult Ph⁻ ALL. This novel protocol achieved an 80.0% CR rate and low toxicity, and warrants further study. In particular, the CR2 rate was favorable for those who experienced late relapse.

For adult patients with relapsed Ph⁻ ALL, the usual treatment is a 4-week reduction chemotherapy regimen consisting of vincristine, corticosteroid, L-asparaginase, and anthracycline. A weekly dose of anthracycline and vincristine for 3 weeks and continuous 4-week corticosteroids cannot be administered owing to serious hematopoietic toxicity and infection during induction therapy[18], which can decrease the elimination of blast cells. Therefore, novel protocols should be studied.

Glucocorticoids (GCs) are a central component of combination chemotherapy for ALL. GCs induce cell death through the GC receptor (GCR), a ligand-induced transcription factor, upon ligand binding and translocation into the nucleus, altering the expression of a large number of genes[21]. GCR expression varies among ALL cells, and GCR expression level in ALL is related to the outcome of glucocorticoid treatment[22–23]. Some studies compared the role of different glucocorticoid doses in the elimination of ALL[19]. Four different corticosteroid doses (prednisolone 40 mg/m^2/d or dexamethasone 6, 18, or 150 mg/m^2/d) were administered for 3 days. The results showed that high-dose corticosteroids (dexamethasone 18 or 150 mg/m^2/d) elicited better responses than standard doses of dexamethasone or prednisone. However, high-dose corticosteroid treatment can also counteract the effect of relative drug insensitivity and low GCR levels. Therefore, in this particular protocol, a daily dosage of 20 mg dexamethasone was employed to enhance the efficacy of reinduction therapy.

Anthracycline is a key component of this protocol. Idarubicin is a new anthracycline that is superior to daunomycin for the treatment of acute myeloid leukemia (AML)[14]. Idarubicin also shows good outcomes in R/R Ph⁻ ALL[15–17]. However, a high dose of idarubicin can lead to a high toxicity-related death rate and poor outcomes. Some studies showed that a total idarubicin dose of 20 mg/m^2 yielded a comparable CR rate to higher-dose idarubicin with a low toxicity-related death rate[17]. Therefore, a total of 30 mg of idarubicin (6–8 mg/m^2, total 10 mg on days 1–3) was used in this study.

With regard to toxicity, this protocol was tolerable among all patients with none experiencing induction death. Hematological toxicities and infections were the most common toxicities during neutropenia but were treatable. These results suggest that this novel protocol is a safe and effective strategy for achieving CR for adult patients with relapsed Ph⁻ ALL. The outcomes are similar to those achieved among newly

diagnosed adult Ph⁻ ALL patients. Therefore, we speculate that this novel induction therapy protocol is equally effective in newly diagnosed adult Ph⁻ ALL patients.

There is currently no optimal therapy for the first salvage regimen in patients with R/R Ph⁻ ALL. Among patients with R/R ALL, remission rates are 18%–44% when treated with traditional salvage chemotherapy, with fewer than 10% of patients alive for 5 years[24]. In recent years, the emergence of new targeted drugs and cell therapies, represented by blinatumomab, inotuzumab ozogamicin, and CAR-T, has significantly improved the outcomes of patients with R/R B-cell ALL. However, some problems still exist. Blinatumomab (Bite) achieves good remission status in adult and pediatric R/R ALL and MRD-positive patients[25], but is not applicable for T-ALL and with significant cost increases, which limits its wide application in clinical practice. CAR-T cell immunotherapy has become a new treatment with good clinical effects for hematological tumors, but still has shortcomings in clinical use, such as the on target/off tumor effects. The limited persistence, a high incidence of early relapse, and serious complications affect the final clinical outcomes of CAR-T[26]. Compared with traditional chemotherapy, Inotuzumab ozogamicin (InO) has a higher CR rate and MRD conversion rate, but the potential hepatic toxicity of InO, especially hepatic sinus obstruction syndrome, limits its wide application in clinical practice[27–28]. Performing allo-HSCT as soon as possible after achieving CR is still the best treatment strategy for R/R ALL.

In summary, this protocol (AALLXQCQC-2019) shows a favorable CR2, with low toxicity and a much shorter chemotherapy duration in adult patients with relapsed Ph⁻ ALL. We suppose that this novel induction therapy is effective in newly diagnosed adult Ph⁻ ALL patients. A prospective, multicenter, randomized controlled clinical trial is ongoing to further indicate the advantage of this induction therapy protocol for newly diagnosed adult Ph⁻ ALL patients.

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