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Efficacy of low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor (CAG regimen) compared to Hyper-CVAD regimen as salvage chemotherapy in relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia

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ABSTRACT

We treated 90 relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph^--ALL) patients with CAG regimen [cytarabine (10 mg/m^2/12 h, days 1–14), aclarubicin (5–7 mg/m^2/day, days 1–8), granulocyte colony-stimulating factor (200 μg/m^2/day, days 1–14)], 82 relapsed/refractory Ph^--ALL patients were treated with increasing aclarubicin dose CAG (5–7 mg/m^2/day, days 1–14, HD-CAG). 96 relapsed/refractory Ph^--ALL patients treated with Hyper-CVAD regimen (control group). After one therapy course, among all groups, there were no statistically significant differences with complete remission (CR) and overall response [OR, CR + partial remission (PR)] rates ($P > 0.05$). In CAG group, CR and OR rates for T-ALL exceeded those for B-ALL ($P = 0.001$, 0.007), while in HD-CAG and control groups, those were not statistically significantly different ($P > 0.05$). CR and OR rates of CAG group for B-ALL were lower than control group ($P = 0.004$, 0.012). Among all groups, there were no statistically significant differences with CR and OR rates for T-ALL ($P > 0.05$). CAG had lesser adverse event than Hyper-CVAD. The overall survival at 3 years for all groups were similar. Efficacy of CAG regimen was similar in comparison to Hyper-CVAD for relapsed/refractory Ph^--T-ALL. HD-CAG could not improve efficacy than CAG regimen.

1. Introduction

In recent years the prognosis for patients with acute lymphoblastic leukemia (ALL) has been improved because use of modern intensive chemotherapy regimens, improved risk-directed treatments, and supportive care has widened [1]. Survival in childhood ALL is approaching 90%, moreover, adaptation of paediatric treatment regimens for use in adult patients has improved 5-year survival to about 50% in some clinical trials [1–3]. However, treatment in adults needs improvement in comparison to children [2,4].

In both children and adults, relapsed and refractory primary ALL still remain the greatest challenges to successful treatment. In adult ALL, more than one-third of all patients and two-thirds of high-risk (HR) patients develop relapse [5]. In contrast, relapse occurs in approximately one-fifth of pediatric patients [6]. The prognosis of relapsed or refractory ALL patients continue to be poor, and long-term survival is only about 10% [5,7–9]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative modality for relapsed/refractory ALL, and the outcome of HSCT is superior when it is performed during complete remission (CR) rather than in patients with active leukemia [7]. Therefore, the primary purpose of salvage therapy is to achieve a second CR in patients with relapsed ALL and the first CR in patients with refractory ALL in order to subsequently perform allo-HSCT as soon as possible [10]. It is very important to explore salvage protocol that can effectively treat relapsed or refractory ALL.

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There is no standard chemotherapy for relapsed or refractory ALL patients. Programs that have been used in salvage include Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) regimen [11], regimens similar to first-line induction [5], high dose cytarabine and anthracycline combinations [12,13], FLAG (fludarabine, cytarabine and granulocyte colony-stimulating factor) regimen [5,14,15], methotrexate and asparaginase combinations [16], and vincristine, dexamethasone and doxorubicin [17]. The best re-induction strategy remains to be determined. In previous studies, we found that the CAG regimen [aclarubicin (ACR), cytarabine (Ara-C) and granulocyte colony-stimulating factor (G-CSF)] showed significant treatment potential for relapsed or refractory ALL, especially for T-ALL patients [18,19]. We have reported that increasing the dose of aclarubicin in CAG (high dose CAG, HD-CAG) regimen can safely and effectively treat relapsed or refractory acute myeloid leukemia (AML) [20]. It is unknown, however, how the therapeutic efficacy of CAG regimen for relapsed or refractory ALL compared with the other salvage regimens and whether increasing the dose of aclarubicin in CAG regimen could improve the therapeutic efficacy compared with the CAG regimen. In this study, we retrospectively summarize 268 patients with Philadelphia chromosome-negative relapsed or refractory ALL to analyze the effect of the CAG regimen and HD-CAG regimen, and compare with patients treated with Hyper-CVAD regimen during the same period.

2. Patients and methods

2.1. Patients

Between April 2004 and February 2014, 268 Chinese patients [male, 182 patients; female, 86 patients; median age, 29 years (range, 3–78)] with Philadelphia chromosome-negative relapsed or refractory ALL treated in The First Affiliated Hospital of Soochow University, Huai'an Second People's Hospital and Xian Yang Central Hospital were enrolled in this study. 90 patients were treated with CAG regimen (CAG group), 82 patients were treated with HD-CAG regimen (HD-CAG group), 96 patients were treated with Hyper-CVAD regimen (control group). All patients were diagnosed with morphological examination, cytochemical, immunophenotypic and cytogenetic analyses. Patient demographics and baseline characteristics are summarized in Table 1. This study was approved by the ethics committee of The First Affiliated Hospital of Soochow University, Huai'an Second People's Hospital and Xian Yang Central Hospital. All patients provided written informed consent before chemotherapy.

2.2. Definitions

In this study, any evidence of disease in the peripheral blood or bone marrow, as well as extramedullary disease, was considered a relapse. The definition of refractory disease referred to not achieving initial remission after two courses of standard induction therapy. The definition of complete remission (CR) referred to a normal bone marrow (BM) aspirate with <5% marrow blasts, absolute neutrophil count $\geq 1 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and no evidence of circulating or extramedullary leukemic blasts. Partial remission (PR) was defined as having <15% but >5% blasts or as having <5% blasts but not reaching the CR criteria for blood cell count or clinical manifestation. Overall response (OR) was defined as CR plus PR. In children patients, complex abnormalities (≥5 types), t(4;11)(q21;q23)/MLL-AFF1 (AF4), near-haploidy were defined as unfavorable karyotypes [21]. In adult patients, complex abnormalities (≥5 types), t(4;11)(q21;q23)/MLL-AFF1(AF4), t(1;19)/E2A-PBX, t(8;14)(q24.1;q32), low hypodiploidy/near triploidy were defined as unfavorable karyotypes [21–26]. Patients who died within the first 8 weeks after start of induction treatment were considered early death (ED). Regimen-related toxicity was graded according to the World Health Organization criteria.

2.3. Treatment protocol

The CAG regimen consisted of Ara-C 10 mg/m^2 injected subcutaneously every 12 h from day 1 to day 14, aclarubicin 5–7 mg/m^2 infused intravenously daily from day 1 to day 8, and G-CSF administered subcutaneously at a dose of 200 μg/m^2/day, unless patient white blood cell (WBC) count was $\geq 20 \times 10^9$/L [18]. The HD-CAG regimen consisted of Ara-C 10 mg/m^2 injected subcutaneously every 12 h from day 1 to day 14, aclarubicin 5–7 mg/m^2 [age ≥ 65 years or had poor performance status (ECOG performance status 3) were treated with aclarubicin 5 mg/m^2] infused intravenously daily from day 1 to day 14, and G-CSF administered subcutaneously at a dose of 200 μg/m^2/day, unless patient WBC count was $\geq 20 \times 10^9$/L [20]. G-CSF subcutaneously was first administered immediately before the first injection of Ara-C, and was stopped 12 h before the last injection of Ara-C. At the time of treatment, if WBC count was $\geq 20 \times 10^9$/L, the administration of G-CSF was postponed. Hyper-CVAD regimen consisted of hyper-fractionated cyclophosphamide, 300 mg/m^2/12 h i.v. over 2 h for six doses, given on days 1–3; vincristine, 2 mg/day i.v., given on days 4 and 11; doxorubicin, 50 mg/m^2/day i.v. over 2 h on day 4; and dexamethasone 40 mg/day i.v., given on days 1–4 and 11–14 [11].

Subsequent post-induction therapy varied according to patients' character. If there was opportunity, allo-HSCT was the first option of post-induction therapy. For patients without suitable donors were available, the younger patients (<60 years) were treated with HD-Ara-c (high-dose Ara-c)/ID-Ara-c (intermediate-dose Ara-c)/VDLP (vindesine, daunorubicin, L-asparaginase and dexamethasone)/CAM (cyclophosphamide, Ara-C and 6-thioguanine)/high-dose MTX (methotrexate) and TA (teniposide, Ara-C)/HD-CAG/hyper-CVAD A or B regimen. The older ALL paitents (≥60 years) were treated with CAM/high-dose MTX and TA/CAG/hyper-CVAD A regimen. In the study, the treating physicians and the patients' medical needs determined supportive measures for optimal medical care. Prophylactic antibiotics, antifungals, and antiviral agents were administered in accordance with institutional guidelines.

2.4. Statistical analysis

Statistical analyses conducted were based on data available from the date of treatment to the date of final patient follow-up on July 31 2014. The categorical comparison of expected values was compared by chi-square test. The following variables groups: patient age, duration of neutrophil $< 0.5 \times 10^9$/L and duration of platelet $< 50 \times 10^9$/L were compared by non-parametric *U*-test. The probability of OS was estimated from the time of treatment according to the Kaplan–Meier method. The log-rank test was used to compare these variables between every group. Statistical analyses performed with SPSS version 16.0 (SPSS, Chicago, IL, USA). All *P* values represented were two sided, results were considered statistically significant when $P < 0.05$.

3. Results

3.1. Patient characteristics

A total of 268 relapsed or refractory ALL patients were enrolled in the study. 90 (33.58%) patients were enrolled in CAG group, 82 (30.60%) patients were enrolled in HD-CAG group, 96 (35.82%) patients were enrolled in control group. Characteristics of patients are shown in Table 1. Among CAG, HD-CAG, and control groups, there were no statistically significant differences with respect to median age, gender, chromosomal aberrations, proportions of patients who were younger than 18, proportions of T-ALL patients or B-ALL patients, and proportions of relapsed patients or refractory patients ($P > 0.05$).

3.2. Efficacy

After one course therapy, as described in Table 1, among CAG, HD-CAG, and control groups, there were no statistically significant differences with CR and OR rates ($P > 0.05$). CR and OR rates of <18 years, T-ALL, relapsed patients, refractory patients, and normal chromosome patients, there were no statistically significant differences ($P > 0.05$), among CAG, HD-CAG, and control groups. CR and OR rates of B-ALL for the CAG group were lower than the control group (CR, $P = 0.004$; OR, $P = 0.012$), however, CR and OR rates of B-ALL were not statistically significantly different for the CAG group and HD-CAG group, HD-CAG group and control group ($P > 0.05$).

In the CAG group, CR and OR rates for T-ALL patients exceeded those for the B-ALL patients ($P = 0.001$ and 0.007, respectively). In the HD-CAG group and control group, CR and OR rates were not statistically significantly different when comparing T-ALL and B-ALL patients (HD-CAG group, $P = 0.093$ and 0.169; control group, $P = 0.347$ and $P = 0.379$, respectively). In the CAG group, HD-CAG group and control group, CR and OR rates were not statistically significantly different when comparing relapsed and refractory patients (CAG group, $P = 0.769$ and 0.769; HD-CAG group, $P = 0.894$ and 0.980; control group, $P = 0.170$ and $P = 0.824$, respectively).

CR rate of unfavorable karyotypes patients for the CAG group were lower than the control group ($P = 0.041$), but there was no