Evaluation of Fludarabine, and granulocyte colony stimulating factor in treatment of efractory/Relapsed Acute Leukemias in adult Iraqi patients

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Abstract

Background: Refractory/relapsed acute leukemia has always been a challenging problem for hematologist. Over the past decade emphasis has been made in the development of regimens containing fludarabine, combined with cytosine arabinoside for the treatment of refractory/relapsed acute leukemias. The aim of this study is to evaluate the efficacy and toxicity of the combination of fludarabine, high dose cytarabine, and granulocyte colony stimulating factor in refractory relapsed cases of acute leukaemia,

Methods: a prospective study is being conducted at the national center of hematology and hematology unit /Baghdad teaching hospital from July 2008 to July 2010.Twenty Patients with refractory/relapsed acute leukemia were treated with fludarabine 30mg/m2 and cytosine arabinoside (AraC) 2 g/m2 for 5 days, and granulocyte colony stimulating factor G-CSF 300 microgram/day from day 0 till neutrophil recovery (ANC >1.0 x 109/l).Response was evaluated by bone marrow examination on day 30-post chemotherapy.

Results: Patients included were refractory acute lymphoblastic leukemia (ALL) (n=5), relapsed ALL (n=4), refractory acute myeloid leukemia (AML) (n=8), relapsed AML (n=3). Complete remission (CR) was achieved in 9(45%) patients, 3 (15%) patients got partial remission. Three (15%) patients died of post chemotherapy complications and 5(25%) patient failed to achieve remission. Major complications encountered were: anemia, fever, bleeding, mucositis and bacterial infections.

Conclusion: FLAG protocol is well tolerated and effective regimen in relapsed / refractory acute leukemias. The toxicity is acceptable, enabling most patients to receive further treatment, including transplantation procedures

Key words: FLAG, refractory acute leukemia, relapsed acute leukemia

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Introduction

Refractory/relapsed acute leukemia has always been a challenging problem for oncologists. Over the past decade emphasis has been made in the development of regimens containing fludarabine, combined with cytosine arabinoside (AraC) for the treatment of acute leukemia, myelodysplastic syndromes (MDS) and the cases of refractory/ relapsed acute leukemias. [1, 2]

Conventional chemotherapy is highly effective in the treatment of acute leukemias. However, relapse develops in 50% to 70% of the cases. Ten percent to 40% of the cases with acute leukemias have primary refractory disease. The management of cases with primary refractory and/or relapsed disease is very difficult. In these cases, complete remission rates are low and remission duration is very short. [3] For this reason, clinical studies with different alternatives are ongoing in cases with relapse and/or refractory acute leukemias. Ara-C is an effective chemotherapeutic agent used in acute myeloblastic leukemia (AML). High-dose Ara-C (HiDAC) regimens have been found to be effective in these refractory/relapse cases.

The rationale of HiDAC is to increase the intracellular Ara-C triphosphate (Ara-CTP) concentration and to augment the cytotoxicity of the drug. One of the chemo resistance mechanisms is the P-glycoprotein (P-gp)-dependent efflux and HiDAC down-regulates the P-gp efflux. [4, 7]. It has been shown that there is a positive correlation between complete response and high intracellular Ara-C content. The combination of Ara-C with fludarabine phosphate increases the Ara-C content two- to sevenfold in leukemic cell. This synergistic effect has been shown in various studies [7]. Ara-CTP content and cytotoxicity increase when HiDAC is given after fludarabine infusion [7,8]. Besides, granulocyte-colony stimulating factor (G-CSF) given in this schema

augments the incorporation of Ara-CTP to leukemic cell DNA and causes an increase in blastic cell death with G-CSF, especially as AML blasts enter the S phase of the cell cycle and cytotoxicity increases. [5,6,8,9,10] For this reason, fludarabine phosphate, Ara-C, and G-CSF regimen (FLAG) is an important choice in cases with refractory/relapsing acute leukemias [5,6,7].

Methods

Twenty patients with refractory/relapsed acute leukemia treated at the National center of Hematology of Almustansiriya University, and Hematology unit / Baghdad teaching hospital are included in this study for the period from July 2008 to July 2010 inclusive.

Eligibility Criteria

Patients with acute leukemias either Acute myeloid leukemia (AML), or acute lymphoid leukemia (ALL) fulfilling the following criteria were eligible for FLAG salvage chemotherapy.

1. Refractory AML cases i.e. patients not responding to Ara-c and anthracycline containing protocol
2. Patients with refractory ALL not responding to either UKALL12 or HyperCVAD protocols
3. Patient with AML relapsing after HiDAC or Midac chemotherapy protocols
4. Patients with ALL with two relapse after UKALL12 and HyperCVAD chemotherapy protocol.
4. Age less than 50 years.
5. Normal renal and liver function tests and left ventricle ejection fraction >55%.

Exclusion Criteria

1. Age more than 50 years.
2. Eastern cooperative oncology group performance status > 2
3. Associated comorbidities e.g liver, renal and heart function impairment

a. ALT >2.0 x N
b. Creatinine >2.0 x N
c. Cardiac ejection fraction <55%

Treatment protocol

Fludarabine 25 mg/m2/d (d1-5) i.v. as a 30-minute infusion, then 4 hours later Ara-C 2 g/m2/d (d1-5) i.v. as a 4-hour infusion ; G-CSF 300 microgram/day was given subcutaneously from day zero until absolute neutrophil count (ANC) >1x 10^9/L.

Response criteria are as follows:

1. Complete remission (CR): Peripheral blood counts within normal limits plus bone marrow blast percentage <5%.
2. Partial remission (PR): Peripheral blood counts within normal limits plus bone marrow blast percentage between 5% and 20%.
3. Refractory disease or no response (NR): No improvement in peripheral blood and/or bone marrow blastic cells.
4. Early death (ED): Death within 6 weeks of chemotherapy.

Empiric broad spectrum antibiotics were started in case of fever higher than 38.5°C for more than 1 hour for one reading or 38.0°C for more than 1 hour for two readings Red cell concentrates and random/single donor platelets were routinely used during post chemotherapy myelosuppression to keep Hb>8.0 g/dl and platelet count >20 x 10^9/L.

Duration of neutropenia and thrombocytopenia was defined as the time (days) from the start of chemotherapy to the day of ANC recovery to more than 1 x 10^9/L and to platelet recovery to more than 100 x 10^9/L, respectively. Toxicity was recorded according to Common Toxicity Criteria (CTC)

Statistical analysis

Patients' data were tabulated and processed using SPSS 15 (Statistical package for social sciences) for windows. Qualitative data are expressed as frequency and percentage, quantitative data as mean and median. Fisher exact test was used for evaluating the significant FLAG regimen response between acute myeloid leukemia and acute lymphoblastic leukemia, and P value ≤ 0.05 regarded significant.

Results

Twenty patients with refractory/relapsed acute leukemia were included in this study. Eleven of them had AML and 9 had ALL. Mean age was 32 (range 20–44) and 26 (range 18–48) in cases with AML and ALL, respectively. Male/female ratio was 1.7/1 in AML and 2/1 in ALL cases. Eight patients 72.7% of the AML cases and 3 patients (33.3%) of ALL cases had refractory disease and rest of them had relapsed disease. (Table 1).

AML cases

Complete remission (CR) was achieved in 6 cases (54.5%). Two cases got partial remission (PR) (18.1%) and 2 cases (18.1%) had no response (NR). Early death(ED) developed in 1 Case (9%). CR was obtained in 3 of 8 cases (37.5%) with refractory disease and 3of 3 (100%) cases with relapsed disease. CR rates to FLAG was not significant in cases between relapse and refractory disease (P = 0.49). PR was obtained in only 2 cases with refractory disease. ED occurred only in 1 of 8 (12.5%) with refractory cases (Table 3).

Grade IV hematological toxicity developed in all cases with AML; median leukocyte nadir was $0.3x10^9$/L (range 0.1–1, 2 $x10^9$/L) and febrile neutropenia developed in all cases.

Median Leukocyte recovery time was 18 days (range 14–34 days). Among 11 cases source of infection can not be determined in 6 cases, 3 cases had pneumonia while the two other cases had E-coli and pseudomonas. ED occurred in 1 case due to hemorrhagic complication.

Nonhematologic complications were mild to moderate nausea, vomiting, and mucositis and could be controlled by routine measures.

ALL cases

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CR and PR were obtained in 3 (33.3%) and 1 (11.1%) of 9 cases, respectively. No response to FLAG obtained in 3 (33.3%) cases and ED occurred in 2 (22.2%) cases. According to the disease status, in cases with refractory disease, CR, PR, NR, and early death (ED) were detected in 1 of 5 (20%), 1 of 5 (20%), 2 of 5 (40%) and 1 of 5 (20%), respectively. In relapsed cases CR, NR, and ED were registered in 2of 4 (50%), 1 of 4 (25%), and 1 of 4 (25%), respectively. CR rate in cases with ALL was higher in relapse cases as compared with refractory cases (50% versus 20% but statistically was not significant (P= 1) (Table 3).

Grade IV hematological toxicity occurred in all cases with ALL, median leukocyte nadir was $0.4x10^9$/L (range$0.1–1.3x10^9$/l) and febrile neutropenia developed in all cases as seen in cases with AML. Median leukocyte recovery time was 16 days (range 12–26). Pneumonia developed in 2 cases; nonspecific pneumonia in 1, and mucormycosis in 1 case. The source of infection can not be determined in other 5 cases. ED was detected in 2 cases; one due to hemorrhagic complication and 1 due to septicemia. Nonhematologic toxicity consisted of nausea, vomiting, and mucositis and could be controlled by supportive therapy.

Median survival was 19 weeks (range 4–36 weeks) in all cases (24 weeks in AML versus 18 weeks in ALL). At present, only 3 patients are alive and 2 of these are in continuous remission. The rest of the patients died because of lack of either autologous or allogenic bone marrow transplantation to consolidate FLAG protocol.

Incidence of FLAG induced toxicity in our patients is shown in Table 3. Overall FLAG was well tolerated with the main toxicity being hematological like anemia and bleeding and non-hematological like gastrointestinal, particularly nausea and vomiting

Table 1. Clinical characteristics of patients.

Parameter	Number
AML	11
Relapsed	3
Refractory	8
Male	7
Female	4
Median age	32range(20–44)
ALL	9
Relapsed	4
Refractory	5
Male	6
Female	3
Median age	26 range(18–48)
Total	20 patients

Table 2 Clinical response rates in all patients.

Patients	CR (%)	PR (%)	NR (%)	ED (%)	P value
AML	6 (54.5)	2(18.1)	2(18.1)	1(9)	
refractory cases	3(37.5)	2(25)	2(25)	1(12.5)	
relapsed cases	3(100)	0	0	0	0.49
ALL	3(33.3)	1(11.1)	3(33.3)	2(22.2)	
refractory cases	1(20)	1(20)	2(40)	1(20)	
relapsed cases	2(50)	0	1(25)	1(25)	1

Table 3. Incidence of hematological and non-hematological chemotherapy induced complications associated with FLAG treatment

COMPLICATIONS	NO. OF PATIENTS
Anemia	18 (90%)
Bleeding	16 (80%)
Fever	20 (100%)
Anorexia	14 (70%)
Nausea	9 (45%)
Vomiting	10 (50%)

mucositis	7 (35%)
Diarrhea	4 (20%)
Liver toxicity	1 (5%)
Conjunctivitis	2(10%))
Death	3 (15%)

Discussion

Although significant advances have been made in the treatment of de novo acute leukemia, the treatment of refractory or relapsed acute leukemia remains difficult. In current medical practice refractory/relapsed cases of acute leukemias and chronic myeloid leukemia in blast transformation are treated with fludarabine containing regimens to achieve the promising results. (11)

CR rates have been increased by combination chemotherapy regimens. However, relapse occurs in the majority of these cases. Relapse disease is a poor condition because of the limited therapeutic choices, low response rates, and short remission duration. The only curative approach in cases with relapse disease is allogenic stem cell transplantation (SCT), and CR status predicts good survival after allo-SCT. For this reason, effective and safe salvage chemotherapy regimen is highly useful in these cases before transplantation. The other important problem is the low probability of an HLA-matched donor. Autologous transplantation is another choice in cases without a donor. However, autologous transplantation results are not good enough and the relapse rate is high in these cases, as seen in the cases in our study. HiDAC has been used and found to be effective in refractory/relapse acute leukemias.(4) On the other hand Ara-C plus fludarabine phosphate combinations have been given to chronic lymphocytic leukemia (CLL) patients first and high response rates have been obtained.(8) Synergistic activity of these 2 agents has been shown by in vitro studies. In experimental studies, it has been shown that intracellular Ara-C concentration has been found to be increased after Fludarabine therapy and, as a result, Ara-C cytotoxicity has been found to be increased. Antileukemic efficacy has been found to be increased after G-CSF addition to this combination.(5,8) Complete remission rates of between 40% and 60% have found been with the FLAG regimen; this combination has mostly been used in cases of AML; and also CR rates up to 50% have been detected in cases of ALL.(5,8,12) The most important limitation of the studies published so far is the low number of patients as in this study. The common results observed in these studies are high response rates and also relatively a low toxicity profile with the FLAG regimen which is consistent with our results. We preferred FLAG regimen due to the low toxicity and theoretically higher response rate. Our results are not different from those in the literature; CR status was found to be 54.4% and 33.3% in AML and ALL, respectively.

Interestingly, we did not find a significant difference in response between refractory and relapsing disease. For this reason, we can suggest that the FLAG regimen can be effectively used in cases of refractory disease as in relapsing disease.

Grade IV hematological toxicity occurred in all cases, and early death occurred in 3 cases due to hemorrhagic complications and septicemia.

Although it has not been advised routinely, prophylactic antibiotics and antifungal drugs and platelet support may be useful in these cases. Although G-CSF was started on 0 day, neutrophil recovery was similar to that reported in the literature for some studies.(5, 6, 8, 10, and 12)

In conclusion, FLAG is a good choice in cases with refractory/relapse acute leukemia as salvage chemotherapy. High efficacy and a low toxicity profile are preferable properties of this regimen, and this regimen has been found to be useful for cytoreduction, especially to candidates for allogenic stem cell transplantation

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