Original Article

FLAG-IDA in the treatment of Refractory/Relapsed Acute Leukaemias: Single Centre Study

Khalil Ullah Hashmi, Badshah Khan, Parvez Ahmed, Shahid Raza, Iftikhar Hussain*, Ahsan Mahmood*, Hamid Iqbal, Hamid Saeed Malik, Masood Anwar

Armed Forces Bone Marrow Transplant Centre and Combined Military Hospital*, Rawalpindi.

Abstract

Objective: To evaluate the efficacy and toxicity profile of the combination of fludarabine, high dose cytarabine, idarubicin, and granulocyte colony stimulating factor in refractory relapsed cases of acute leukaemia, a study is being conducted at Armed Forces Bone Marrow Transplant Centre (AFBMTC) Rawalpindi since January 2003. Data up to June 2004 (early report) is being presented.

Methods: Twelve Patients with refractory/relapsed (Ref/Rel) acute leukaemia (AL) were treated with fludarabine 30mg/m2 and cytosine arabinoside (AraC) Arac 2 g/m^2 for 5 days, idarubicin 10mg/m^2 for 3 days, and granulocyte colony stimulating factor G-CSF 5 micro g/kg from day 0 till neutrophil recovery (ANC >1.0 x 10^9/l). Response was evaluated by bone marrow examination on day 20-post chemotherapy.

Results: Patients included were refractory acute lymphoblastic leukaemia (ALL) (n=2), relapsed ALL (n=3), refractory acute myeloid leukaemia (AML) (n=3), secondary AML (n=2) relapsed AML (n=1) and acute undifferentiated leukaemia (AUL) (n=1). Complete remission (CR) was achieved in 8 (66.6%) patients. Three (25%) patients died of post chemotherapy complications and one patient failed to achieve remission. Out of 8 patients who achieved CR, 4 underwent allogeneic bone marrow transfusion (BMT), 1 is being evaluated for the same, 1 received idorubicin, AraC and etopuside (ICE) and high dose AraC, 1 did not receive further chemotherapy and 1 relapsed two months after remission. Seven patients are still in CR after a median follow up of 8 months (range 3-18). Major complications encountered were diarrhoea, mucositis, toxic ileus, transient hepatic toxicity, fungal and bacterial infections.

Conclusion: In our experience, FLAG-IDA is well tolerated and effective regimen in relapsed / refractory acute leukaemias. The toxicity is acceptable, enabling most patients to receive further treatment, including transplantation procedures (JPMA 55:234;2005).

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 (FDR), combined with cytosine arabinoside (AraC) for the treatment of acute leukaemias, myelodysplastic syndromes (MDS) and the cases of refractory/relapsed acute leukaemias.[1,2] Fludarabine and AraC (FA) were first investigated in 1991. In 1992 granulocyte colony stimulating factor (G-CSF) was added to fludarabine and AraC combination to form FLAG. Subsequently Idarubicin (Ida) was combined with FA and given with or without G-CSF. After original use in 1997, at least partly as a result of these trials, FA, FLAG, FLAG -Ida have found widespread use in haematological malignancies.[3-5]

The FLAG and FLAG- Ida regimens, have recently been used with encouraging results in poor risk acute myeloid leukaemia (AML), MDS and refractory or relapsed acute lymphoblastic leukaemia (ALL).[6-8] The toxicity of this combination regimen was also found to be acceptable. The rationale for these regimens is the synergistic action between the various agents. FDR triphosphate, the active metabolite of FDR, inhibits ribonucleotide reductase with subsequent accumulation of intracellular AraC triphosphate.[9,10] A positive correlation has been found between intracellular AraC triphosphate levels and remission rates. G-CSF prior to FDR increases the fraction of cells in cycle when they are most vulnerable to AraC and enhances the incorporation of AraC into DNA.[11,12] Idarubicin is used because it was found to be less susceptible to multidrug resistance compared with other anthracyclines in human leukaemia cell lines.[13,14]

In majority of AML as well as a significant number of ALL cases, multiple genes and pathways associated with treatment failure have been identified. Interestingly, nearly 100 genes were determined to be significantly associated with treatment failures. Majority of the 20 most significant genes associated with treatment failure are those involved in specific signal transduction pathways. In acute leukaemias and other haematological malignancies, relapse is associated with the emergence of resistant clones of cells. Several regimens achieve broadly similar results. For patients who enter complete remission, the overall relapse risk is now 45-50%, but this is highly variable and is primarily determined by the biology of disease.[15]

In childhood acute lymphoblastic leukaemia (ALL) overall event free survival (EFS) and survival rates are 80%, with contemporary treatment strategies based on biologic and clinical risk factors. However, at relapse, despite intensified risk-adapted chemotherapy, overall cure rates of only 35% are achieved.[16] Patients who fail initial induction attempts are rarely, if ever, cured with subsequent chemotherapy. Haematopoietic Cell Transplantation (HCT) has been reported to cure 10-20% of such patients.[17]

Patients and Methods

Eligibility Criteria

Patients with AML, ALL and chronic myeloid leukemia (CML) in blast transformation fulfilling the following criteria were eligible for FLAG-Ida reinduction chemotherapy.

1. Failure to respond (Refractory Disease) to remission / induction therapy containing AraC + anthracycline.
2. Patients with Acute Lymphoblastic Leukaemia (ALL) relapsing while on maintenance.
3. Patient with Acute Myeloid Leukemia (AML) relapsing within 6 months of remission/induction chemotherapy.
4. High risk Acute Leukaemias
   a. AML evolving from myelodysplastic syndrome.
   b. CML in blast transformation /evolving into Acute Leukaemia.
   c. Acute Undifferentiated Leukaemia (AUL)
5. Age less than 50 years.

Exclusion Criteria

1. Patient older than 50 years of age.
2. ECOG performance status >2
3. Severe organ damage
   a. ALT >2.0 x N
   b. Creatinine >2.0 x N
   c. Cardiac ejection fraction <60%
4. Patients who relapsed after remission/induction with FLAG-Ida.

We started the study since January 2003. Data up to June 2004 is being presented. During this period 15 cases of refractory/relapse acute leukemia fulfilling the above criteria were treated. Out of which 12 cases received FLAG-Ida. These included Refractory ALL(n=2), Relapsed ALL (n=3), Refractory AML (n=3), Secondary AML (n=2) Relapsed AML (n=1) and AUL (n=1) (Table 1).

Refractory ALL patients were those who did not respond to conventional remission/induction chemotherapy including daunorubicin, vincristine, prednisolone and L-asperginase as per UK ALL 12/UK ALL 97 modified 99 paediatric protocols. Whereas refractory AML cases were those not responding to conventional chemotherapy including cytarabine, etoposide and daunorubicin or mintoxantrone according to UK MRC AML 12 protocol. Three cases of ALL were those who relapsed at 2, 4 and 7 months while on maintenance therapy (average period of relapse 4.3 months) whereas 1 case of AML relapsed within six months of 4th intensification chemotherapy course (MidAC). One case of secondary AML was transformed from CML, whereas 1 patient evolved from myelodysplastic syndrome (MDS). A newly diagnosed patient of acute undifferentiated leukemia was also included in the study.

After complete evaluation all these patients were subjected to FLAG-Ida chemotherapy consisting of fludarabine 30mg/m^2 IV infusion over 30 minutes followed by AraC 2g/m^2 IV infusion over 4 hours, 4 hours after the completion of fludarabine infusion for 5 days, idarubicin 10mg/m2 IV infusion over 30 minutes, 30 minutes post AraC infusion on day 1, 3, 5 and G-CSF S/C 5µg/kg from day 0 until neutrophil recovery (ANC >1.0 x 10^9/L). The patients were treated in laminar airflow rooms, a protected environment whenever such rooms were available. All patients routinely received trimethoprim /sulphamethoxazole, INH and fluconazole as prophylaxis against, pneumocystis carinii, tuberculosis and fungal infections respectively. 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.

Criteria for the assessment of remission status were based on bone marrow (BM) examination showing <5% blasts, done at day 20 post chemotherapy or when ANC>1.0x10^9/L. Reinduction was to be offered with second course of FLAG-IDA to patients having persistent disease. Criteria for persistent disease are based on Day +20 BM examination findings, (>20% blasts in a marrow having at least 20% cellularity).

Criteria for relapse status is >5% blasts in the marrow, 30, 60 and 90 days after achieving complete remission with FLAG-Ida chemotherapy. Patients achieving complete remission would be subjected either to allogeneic Stem Cell Transplant (SCT) on the availability of HLA matched sibling donor, or consolidation/intensification chemotherapy.

Results

Out of 12 patients who were included in the study, 9 were male and 3 were female (M:F ratio 3:1). Age ranged from 8 years through 46 years (median age 24 years). Complete Remission (CR) was achieved in 8 patients (66.6%). One patient failed to achieve remission but reverted back to original disease (MDS). One patient of relapsed ALL went into second relapse 2 months after achieving complete remission, with FLAG-Ida. Whereas three (25%) patients died of post-chemotherapy complications. One had prolonged myelosuppression complicated by septicaemia and ARDS. Whereas 2 patients died of intracerebral haemorrhage (Table 1).

Out of 8 patients who achieved CR, 4 received, allogeneic stem cell transplantation and one case is being evaluated for allogeneic stem cell transplantation. One patient received two further courses of chemotherapy with ICE and high dose AraC. One patient could not afford further chemotherapy however she is still in remission. Seven patients are at present still in CR after a median follow up of 8 months (range 3-18).

Table 1. Distribution of diseases, with individual CR rates, mortality, amongst the 12 patients treated with FLAG-Ida over a period of 1½ year.

Disease	No. of patients (n=12)	Failure to achieve CR (n=4)	CR (n=8)	Relapsed after CR (n=1)	Overall CR (n=7)	Mortality (n=3)
AML						
Refractory	3	1/3	2/3		2/3	1/3
Relapsed	1		1/1		1/1	
ALL						
Refractory	2		2/2		2/2	
Relapsed	3	1/3	2/3	1/2	1/3	1/3
Secondary						
From CML	1		1/1		1/1	
From MDS	1	1/1	0/1		0/1	
AUL	1	1/1	0/1		0/1	1/1

CR: Complete remission; CML: Acute myeloid leukaemia; ALL: Acute Lymphoblastic leukaemia; CML: Chronic myeloid leukaemia; MDS: Myelodysplastic syndrome; AUL: Acute undifferentiated leukaemia.

The early hematological recovery assessed by ANC>1.0x10^9/L and platelets >20x10^9/L required a median duration of 23 days (14-35) and 25 days (16-42) from the start of chemotherapy. Fever >38^0 C was observed in 8 of 12 cases (66.6%). Six (50%) had fever for which cause could not be identified and 2 documented infection with Candida (isolated from blood and bronchial secretions). Whereas 1 had Pseudomonas infection (isolated from abscess in the xiphisternal area).

Incidence of FLAG-Ida induced toxicity in our patients is shown in Table 2. Overall FLAG-Ida was well tolerated with the main toxicity being gastrointestinal, particularly nausea and vomiting.

Table 2. Incidence of non-haematological chemotherapy induced complications associated with FLAG-Ida treatment .

Toxicity	Incidence (n=34)
Nausea	12 (34)
Vomiting	8 (24)
Diarrhoea	4 (12)
Mucositis	6 (18)
Toxic Illeus	2 (6)
Hepato toxicity	2 (6)

Percentage values are given in parenthesis.

Discussion

Although significant advances have been made in the treatment of de novo acute leukaemia, the treatment of refractory or relapsed acute leukaemia remains difficult. In current medical practice refractory/relapsed cases of acute leukaemias, and chronic myeloid leukaemia in blast transformation are treated with fludarabine containing regimens to achieve the promising results.[18]

Since January 2003 we have treated the majority of such patients, and others with high-risk haematological malignancies, with FLAG-Ida. The data presented is an analysis of 12 cases of high-risk acute leukaemia cases treated with FLAG-Ida at our institution over 1½-year period between January 2003 and June 2004, representing an early report of this treatment modality in refractory/relapsed acute leukaemias in Pakistan.

The results show that FLAG-Ida is an effective remission induction regimen for poor prognosis acute leukaemia patients not responding to conventional chemotherapy. These patients were either a very poor risk group including 41.6% with primary refractory disease (ALL=2, AML=3), 33.3% with relapsed disease (ALL=3, AML-1) and 25% with high-risk disease (CML in blast transformation, AML evolved from MDS and AUL - one

Table 3. CR rates of primary refractory (Ref) and relapsed (Rel) acute leukaemia (AL) from other published studies19.

Disease	Treatment	Numbers	CR rate %	Reference
Ref and first Rel AML	Various regimens	243	33	Keating et al (1989)
Ref and Rel AML	ICE	97	43	Carella et al (1993)
Ref AML	Ida +ID araC	21	52	De Witte et al (1996)
First Rel AML	MEC	50	68	Vignetti et al (1996)
Ref and first Rel AML	Timed sequential MEC	20	60	Martino et al (1999a)
Ref and first Rel AML	HD araC + mitoxantrone	162	38	Karanes et al (1999)
Ref and first Rel ALL	RELAL-88	45	74	Martino et al (1999b)
Ref and first Rel ALL	Various regimens	314	31	Thomas et al (1999)
Ref and Rel AL	HD araC +HD mitoxantrone	66	53	Raanani et al (1999)

HD, high dose; ID, intermediate dose;ICE, idarubicin, araC and etoposide; MEC, mitoxantrone, etoposide and araC; MAE, mitoxantrone, HD araC and etoposide; RELAL-88, vindesine, mitoxantrone, cyclophosphamide, ID araC, prednisolone and methotrexate. AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia

Table 4. CR rates and mortality in refractory (Ref) and relapsed (Rel) Acute Leukaemia (AL) with FLAG-Ida chemotherapy from other published studies.

CTR	Disease	Numbers	CR rate %	Mortality %	EFS (Months)	Reference
Royal free Hosp UK	AL MDS	105	59	17	11	Virchis A et al (2004)[19]
University of Bari Italy	Ref and Rel AL	46	52.1	6.6	12	Pastore D et al (2003)[20]
University of Genova Italy	AL	42	82	2	17	Clavio M et al (2002)[21]
University of Genova Italy	Secondary AL	42	33	14	16	Clavio M et al (2001)[22]
Norfolk and Norwich Hosp UK	Ref and Rel ALL	8	87.5	-	24	Deane M et al (1998)[7]
Kings College School of Med and Dentistry London	High Risk MDS/AML	10	63	36.8	10	Parker JE et al (1997)[6]
University of Wales College of Med UK	AML	72	78	-	8	Kell WJ et al (2003)[23]
University Bonn Germany	Ref /Rel Secondary AML	23	73.9	4.3	13.5	Fleischhack G et al (1998)[8]
Istanbul University Turkey	Rel and Secondary AL	17	17.6	41.1	-	Yalman N et al (2000)[24]

case each). The complete remission was achieved in 8/12 (66.6%) with median event free survival of 8 months. Three patients (25%) died of therapy related complications like septicemia, ARDS and CNS haemorrhages.

Different studies with other chemotherapy regimens have shown a CR rate ranging from 31-74%.[19] Our results of achieving CR rate of 66.6% favourably comparable with these findings (Table 3).

We also compared our data with studies carried out with FLAG-Ida in Refractory/ Relapsed acute leukaemias. The published data is variable.[19-25] Yalman N et al (2000) had a CR rate of 17.6% with the mortality rate of 41%, where as Deane M et al (1998) from Norfolk and Norwich Hospital UK achieved 87.5% CR rate. CR rate of 66.6% in our study is quite encouraging. The mortality rate is 25% in our study which is also comparable with the published dat (Table 4).[19-25]

At present the number of patients in our study is small as well as over all duration of follow-up is short. However the study is ongoing, the long-term disease free survival will be established after follow-up of these cases. In addition more patients will be included in the study and the effectiveness of this treatment approach would be better assessed.

In this study the median duration of neutrophil and platelet recovery was 23 and 25 days respectively, which is

slightly prolonged as compared to other studies because of neutropenic febrile illnesses with recurrent infections in our cases. Incidence of fungal and Pseudomonas infection reflects the immunosuppressive property of FDR.

Studies suggest that early HCT following reinduction chemotherapy is an effective treatment strategy in such high-risk patients.[25] In our study patients having HLA matched sibling donor underwent HCT with significant improvement in survival with maximum duration 15 months. Second remission in these cases is likely to be short-lived, therefore strong consideration should be given to HLA typing of all these patients on their families at the earliest.

In conclusion FLAG-IDA is an established and well-tolerated remission/induction regimen in high risk acute leukaemias and offers a window of opportunity for HCT. This regimen appears to be more myelotoxic as compared to other conventional remission/induction chemotherapy. However the toxicity is acceptable which enables most of the patients to receive further treatment, including HCT.

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