



Fludarabine-based salvage therapy for refractory/relapsed acute leukemias: A single center experience

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Introduction

First line regimens for the treatment of adult acute leukemias are highly effective in achieving initial remission, however, relapse is seen in about half of cases [1]. Around 20–30% of these cases are refractory to conventional treatment, becoming a challenging domain for the heme-oncologists [2, 3]. The primary strategy for these cases is reinduction chemotherapy followed by allogenic stem cell transplantation [4, 5]. Fludarabine, a purine nucleotide analog, has recently become the focus of treatment for acute leukemias and myelodysplastic syndromes (MDS). Its active metabolite, Fludarabine triphosphate, inhibits ribonucleotide reductase with subsequent accumulation of intracellular cytosine arabinoside (AraC) triphosphate [6, 7].

The toxicity profile of Fludarabine has been shown to be acceptable [8], but it is often combined with additional agents to improve efficacy and limit untoward toxicity [9–11]. The combination of Fludarabine with Ara-C increases the intracellular Ara-C content by two- to seven-fold in leukemic cells, which has shown a positive correlation with remission rates [12]. Idarubicin (IDA), an anthracycline, is also added because of its less susceptibility to multidrug resistance compared to other anthracyclines in human leukemia cell lines; and have lesser cardiotoxicity making them favorable for heavily pretreated patients [13, 14]. Granulocyte colony stimulating factor (G-CSF) prior to Fludarabine increases the fraction of cells in cycle when they are most vulnerable to AraC, and enhances the incorporation of AraC into DNA [15, 16].

The synergistic action of Fludarabine, AraC and IDA with or without G-CSF (abbreviated as FLAG-IDA and FLA-IDA respectively) have found widespread use as salvage chemotherapy for refractory/relapsed Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) with complete remission rates ranging from 40–60% with variable 30-day mortalities ranging from 4% to 9% [4, 5, 17, 18]. Additionally, a

recent retrospective trial by Farooq et al. [19] compared outcomes in 76 patients treated for FLAG-IDA and FLAG; and found a significant improvement in survival in patients treated for Fludarabine-based regimen without IDA [19].

However, a small single-center study from Pakistan by Hashmi et al. [20] found a much higher 30-day mortality rate of 25% (3/12 patients) with FLAG-IDA and similar complete remission rates (66%). Hence, the purpose of our study is to identify the 30-day mortality rate in a larger cohort of patients with ALL/AML being treated with Fludarabine-based regimens in a single tertiary care center in Pakistan. Additionally, we aim to compare outcomes in adult patients with ALL/AML being treated with Fludarabine-based regimens with and without G-CSF, since this comparison has previously been performed without the addition of IDA in treatment regimens [9]. We hypothesize the 30-day mortality rate with Fludarabine-based regimens will be lower than the previously published 25% and there will be a significant difference in post-treatment outcomes between patients being treated with FLA-IDA and FLAG-IDA.

Methods

This retrospective cohort study was reviewed and approved by the Aga Khan University Hospital Ethical Review Committee. Electronic medical records were searched from January 2015 to November 2020 from one tertiary university hospital in Karachi.

Study population

Medical records were searched for male and female adult patients being treated with Fludarabine-based therapy for: 1) Refractory/Relapse ALL; 2) Refractory/Relapse AML; or 3) Acute Leukemia transforming from MDS and Chronic Myeloid Leukemia refractory to or relapsing after

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first line regimen. Patients were excluded if they: 1) were <18 years or >60 years of age; 2) had ECOG status >2 [21]; 3) had severe organ damage defined as alanine transaminase (ALT) >2.0x normal or creatinine >2.0x normal or cardiac ejection fraction <60%; or 4) had previously been on Fludarabine-based treatment.

Data collection

The following demographics were extracted from medical records: patient age, sex, refractory/relapse acute leukemia (ALL or AML), molecular genetic risk factors (FLT3 for AML and BCR ABL for ALL), cytogenetic risk factor and clinical risk stratification (high or low on ALL or AML risk stratification score) [22, 23]. The following post-intervention variables were extracted: 1) complete remission on day 28 of chemotherapy; 2) incidence of early death (defined as death within 4 weeks of chemotherapy); 3) incidence of relapse at 30 days, 60 days and 90 days after achieving complete remission at the end of 4-week of treatment; and 4) toxicity profile according to the Common Terminology Criteria for Adverse Events (CTCAE) which included nausea, vomiting, diarrhea, anemia, hepatotoxicity and nephrotoxicity [24].

Fludarabine-based treatment regimens

Patients were divided into the following groups based on chemotherapy regimen received:

FLA-IDA: This regimen included intravenous Fludarabine given at 30 mg/m²/day in a 30-minute infusion (for Day 1–5), then 4 h later with intravenous AraC at 2 g/m²/day (for Day 1–5) in a 4-hour infusion and intravenous IDA at 8 mg/m²/day (for Day 1–3) as a 30-minute infusion. These patients did not receive G-CSF throughout the course of treatment.

FLAG-IDA: This regimen also included Fludarabine (30 mg/m²/day for Day 1–5), AraC (2 g/m²/day for Day 1–5) and IDA (8 mg/m²/day for Day 1–3); with the addition of subcutaneous G-CSF from Day 1 to until absolute neutrophil count (ANC) of 500/mL.

Main outcome measure and definitions

The following outcome measures are recorded:

Complete remission: Defined as having peripheral blood counts within normal limits plus bone marrow blast percentage <5% at Day 28 bone marrow biopsy.

Relapse: Defined as having >5% blasts in the bone marrow at either Day 30, 60 or 90 after achieving complete remission on Day 28 bone marrow biopsy.

Refractory disease: Defined as having persistence of blast cells in peripheral blood and/or >5% bone marrow blast cells at Day 28 bone marrow biopsy.

Statistical analysis

Analysis was based on per protocol analysis. Univariate statistics were performed and 30-day mortality was calculated for the entire sample. Patients were categorized in the following groups based on treatment regimens; FLA-IDA or FLAG-IDA. Group wise comparisons were performed, continuous variables were compared using non-parametric *t*-tests and categorical variables were compared using χ^2 test (Fisher's Exact for group $n < 5$). Groups were compared on initial presentation characteristics and post-therapy outcomes. A binary logistic regression model was built with stepwise selection to identify initial presentation characteristics and treatment regime that would be predictive of complete remission on Day 28 of chemotherapy. A Kaplan Meier life table stratified by treatment regime was made. Patients who did not have remission were labeled as failure during treatment. Patients who had remission on the Day 28 biopsy but had a relapse on subsequent follow-up visits were label as failure on Day 30, 60 or 90 post-remission

respectively. Patients who had remission but did not have a relapse during the 3-month follow-up period were censored at Day 90 and labeled as not having failure of treatment. Survival analysis was performed using a Log-rank test comparing the equity of survival functions. A *p*-value of 0.05 was considered significant and analysis was performed on R Programming Language [25].

Results

From January 2015 to November 2020, 39 patients were diagnosed with refractory/ relapsing acute leukemias and were treated with fludarabine-based therapy. Patients were a mean of 34.6 ± 10.6 years (range 19 – 55 years) and were 77% male. One patient left against medical advice before treatment and was not included in analysis. Three patients died during the chemotherapy regimen and were considered as Early Death during intervention, leading to a 30-day mortality rate of 8% (3/38). Out of the 38 patients, 17 were treated with FLA-IDA and 21 were treated with FLAG-IDA. All patients had undergone bone marrow cytogenetics at baseline. Patients with no abnormality in karyotype were considered normal in cytogenetic analysis, while those with one or more abnormalities, including complex karyotype were counted as abnormal. 63% (24/38) patients in the study had at least one abnormality in their karyotype.

Molecular genetic risk was based on the presence of FLT3-ITD mutation in acute myeloid leukemia patients and BCR-ABL fusion in acute lymphoblastic leukemia patients. FLT3-ITD was positive in 5% (1/19) of all AML patients while BCR-ABL was positive in 23.8% (5/21) of the ALL patients in our sample population. NPM1 mutation was found to be positive in 10% (2/20) of AML patients. NPM1, FLT3-ITD mutation and BCR-ABL fusion was performed by RT-PCR technique. Patients did not differ in age, sex, primary diagnosis, history of refractory disease, clinical risk stratification, cytogenetic analysis or molecular genetic risk. Group wise patient demographics are presented in Table 1.

When comparing outcomes between regimens, 1 patient in the FLA-IDA group and 2 in the FLAG-IDA group died within 4 weeks of intervention; hence only 16 patients in FLA-IDA and 19 in the FLAG-IDA group were included in all subsequent outcome comparisons. Groups did not significantly differ in post-therapy outcomes or toxicity profile, except FLA-IDA had a significantly higher proportion of hepatotoxicity than FLAG-IDA ($p = 0.006$) post-therapy. There were no clinical features including co-morbidities, viral infections or underlying disease that could be attributed to the hepatotoxicity in the FLA-IDA group. It was an incidental finding that was noticed during the retrospective analysis in the study. Group wise outcomes are presented in Table 2.

Table 1
Sample group-wise demographics.

	FLA-Idan = 17	FLAG-Idan = 21	<i>p</i> -value
Age	35.65 ± 10.8 years	34.29 ± 10.5 years	0.772
Sex	5 female, 12 male	4 female, 17 male	0.703
Primary Diagnosis	8 de novo AML 6 de novo B-ALL 3 de novo T-ALL 1 secondary B-ALL	9 de novo AML 4 de novo B-ALL 5 de novo T-ALL 1 secondary B-ALL 1 tdT + lymphoma 1 myeloid sarcoma	0.739
Primary Leukemia Type	8 myeloid 9 lymphoid	10 myeloid 11 lymphoid	0.973
Cytogenetic Analysis	12 abnormal	12 abnormal	0.393
Molecular Genetic Risk	2 high risk	4 high risk	0.672
History of Refractory Disease	2 refractory disease	6 refractory disease	0.257
Clinical Risk Stratification	10 high risk	16 high risk	0.307

Table 2
Post-therapy Outcomes by Treatment Regime.

	FLA-IDA n = 17	FLAG-IDA n = 21	p-value
Early Death	1/17	2/21	>0.999
Febrile	16/16 Grade 3	19/19 Grade 3	–
Nausea	2/16 Grade 2 1/16 Grade 3	2/19 Grade 2	0.526
Vomiting	1/16 Grade 3	1/19 Grade 2	0.362
Diarrhea	1/16 Grade 3	–	0.457
Hepatotoxicity	5/16 Grade 1 2/16 Grade 2 1/16 Grade 3	–	0.006
Nephrotoxicity	–	1/19 Grade 1 1/19 Grade 2	0.409
Allergy	–	–	–
Anemia	5/16 Grade 1 4/16 Grade 2 7/16 Grade 3	6/19 Grade 1 10/19 Grade 2 3/19 Grade 3	0.133
Complete Remission after therapy	10/16	8/19	0.229
Relapse within 90 days after Remission	5/10	4/8	–

On logistic regression, not having a molecular genetic risk factor was the only significant predictor of complete remission after treatment with Fludarabine-based regimens. Of note, type of Fludarabine-based regimen was not a predictor for complete remission ($\beta = 1.00, p = 0.309$). Results of logistic regression are presented in Table 3.

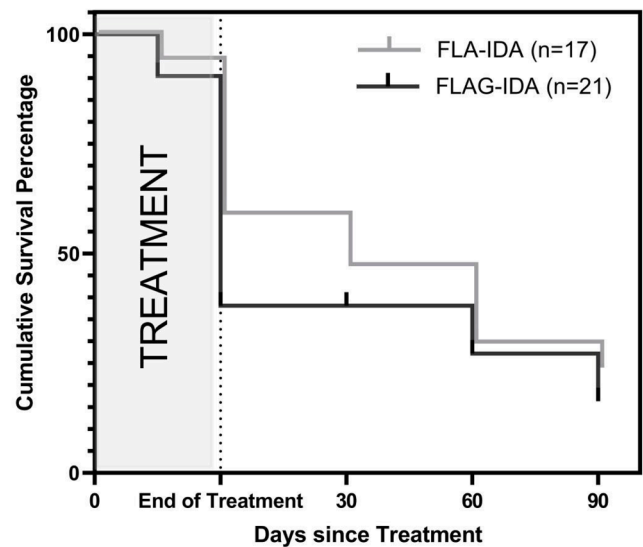
Lastly, there was no significant difference in survival between Fludarabine-based regimens up to Day 90 ($p = 0.671$). About 60% of patients in the FLAG-IDA group and 40% of FLA-IDA did not achieve complete remission after therapy, and showed similar patterns of relapses up to Day 90. Kaplan Meier life table showing cumulative survival are presented in Fig. 1.

Discussion

Our retrospective study of patients with relapsed ALL or AML being treated with Fludarabine-based chemotherapy had several insightful results. With respect to our primary objective, we found a 30-day mortality rate of 8%, which is much lower than the 25% reported in a previous study from a similar setting [20]. Complete remission after therapy was observed in half of the sample (18/35) which is consistent with previous studies [4, 5, 17, 18]. With respect to our secondary objective, we did not find any difference in survival between patients on Fludarabine-based regimens with and without G-CSF, however, patients on FLAG-IDA has a significantly higher incidence of post-treatment hepatotoxicity that was not observed in patients treated with FLA-IDA. Temporary elevation of hepatic enzymes occur in about 10–29% of patients receiving G-CSF, however, these return to normal once

Table 3
Results of Logistic Regression predicting Complete Remission within 4 weeks.

	β Coefficient	Standard Error	Wald-score	p-value
Molecular genetic risk factor (present vs. not present)	–3.614	1.711	4.461	0.035
Risk Stratification (high/intermediate vs. low)	2.131	1.098	3.765	0.052
Cytogenetics (abnormal vs. normal)	–0.064	0.974	0.004	0.947
Age	0.012	0.036	0.116	0.733
Gender (male vs. female)	1.830	1.251	2.139	0.144
Leukemia type (AML vs. ALL)	1.546	1.074	2.072	0.150
Chemotherapy Regimen (FLA-IDA vs. FLAG-IDA)	1.002	0.985	1.035	0.309
Initial disease presentation (Refractory vs. non-refractory)	0.563	0.989	0.324	0.569



Log rank test comparing survival function $\chi^2 = 0.18, p = 0.671$

Fig. 1. Kaplan Meier life table stratified by Fludarabine-based treatment regimen. Log rank test comparing survival function $\chi^2 = 0.18, p = 0.671$.

treatment is discontinued [26].

When investigating pre-treatment demographics and clinical risk factors that would be predictive of remission after 4 weeks of Fludarabine-based chemotherapy, our analysis found the presence of molecular genetic risk factors (FLT3 for AML and BCR-ABL for ALL) to be predictive of poor outcomes. FLT3 is a FMS-like tyrosine kinase gene mutation and is present in about 30% of patients with AML, and is associated with shorter remission duration and higher relapse rates compared with patients without the mutation [27]. Similarly, the presence of the fusion of BCR-ABL is present in about 30% of patients with ALL and is associated with a lower chance of initial treatment response and a lower probability of disease-free survival [28]. Other variables, such as clinical risk stratification, patient gender and leukemia type (lymphoid versus myeloid), were showing a trend in our logistic regression, however, our sample size is not large enough to make meaningful conclusions. Larger, adequately powered studies are required in the future to investigate which demographic and clinical risk factors are most predictive of treatment success during the 4-week intervention.

Advancements in treatment of de novo acute leukemias are underway. First line regimens commonly used in our setting are AraC and IDA as 7 + 3 regimen in AML while the UK-ALL XII protocol is used for ALL patients [29]. Yet, the treatment of refractory/relapsed leukemias are a difficult domain due to low response rate, shorter duration of remission, high treatment related mortality and narrow range of therapeutics available, and the best modality of treatment is to do an allogeneic stem cell transplant [4, 5]. For these reasons, salvage chemotherapy like Fludarabine in combination with other chemotherapeutics with an acceptable toxicity profile is highly useful for bridging patients to stem cell transplant or at least help them achieve second remission that can be followed with consolidation chemotherapy. Novel agents for leukemias refractory to Fludarabine-based regimens are also underway. Blinatumomab is a bispecific T cell engager monoclonal antibody that is directed at both CD19 on precursor B cell ALL cells and CD3 on cytotoxic T cells. It is approved by the European Medicines Agency for treatment of relapsed/refractory Philadelphia chromosome (Ph) negative precursor B cell ALL. The US Food and Drug Administration has also approved it for relapsed/refractory Ph-negative and Ph-positive precursor B cell AL. A phase III trial has shown significantly longer overall survival than chemotherapy [30]. However, the unavailability and cost of this drug is a major hindrance for use in low income countries. Clofarabine, a

second-generation purine nucleoside analogue, has shown some promising results for ALL in Phase 2 trials in the pediatric population [31], and has also shown activity against AML, MDS and chronic myeloid leukemias in blast phase [32, 33]. Nelarabine, an araguanosine analogue, has also shown to be very active as a single agent in relapsed or refractory T-lineage ALL and may also be useful for Fludarabine-resistant leukemias [34].

This study has several limitations. This is a retrospective study and hence we cannot determine causality, prospective trials should be designed in the future to control for additional factors associated with treatment outcomes. More studies with larger sample size and prospective analysis would help us ascertain risk factors that predict the clinical outcomes. We also have a relatively small sample size with a short follow-up of 90 days after end of chemotherapy. Future studies should perform a longer follow-up to see the outcomes after allogeneic stem cell transplantation. Nine patients from our sample remained in remission up to Day 90 after achieving complete remission on Day 28. However, not all patients ended up having a transplantation with the major limiting factor being financial issues, unavailability of matched donors and personal choice. These factors are common barriers to treatment of cancers in low- and middle-income countries [35], so it is not unexpected to also find them in our setting. Future studies should investigate the common barriers to treatment implementation for acute leukemias in a low-income setting.

Conclusion

This retrospective study found the 30-day mortality rate for Fludarabine-based regimens for adult acute leukemias to be 8%, complete remission in 51% of the patients with an acceptable side-effect profile. This makes it a reasonable choice as salvage chemotherapy to bridge to stem cell transplant for cases with refractory/relapsed leukemia. We also did not find any difference in outcomes between the two treatment regimens, FLA-IDA and FLAG-IDA, so both appear equally efficacious and safe for the treatment of refractory/relapsed acute leukemias. Good efficacy and manageable toxicity profile are the ideal properties of this regimen and should be considered to salvage patients until new therapies in development are available.

Declaration of Competing Interest

The authors do not declare any relevant conflicts of interests.

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