"Clinical Outcome of Patients with Relapsed / Refractory Acute Leukemia Treated with FLAG-IDA Regimen"

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ABSTRACT

Background: **Patients with Refractory/Relapsed (R/R) acute leukemia (AL) have a poor prognosis.** Objective: **We aimed to evaluate the chemotherapy regimen fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) in patients with R/R AL.** Patients: **We studied 33 patients with R/R AL. Distribution of the AL subtype was: myeloblastic n=17 (52%), lymphoblastic n=14 (42%),) and biphenotypic n=2 (6%).** Results: **Complete remission (CR) was achieved in 15 cases (45.5%) and seven patients dead resulting in a mortality of 21.1%. In patients with hematological recovery the median time to neutrophils recovery (> 0.5 x 10^9/l) was 24 days (range 10-38); platelet levels of more than 20 x 10^9/l and 50 x 10^9/l were reached in a median time of 24 (range 17-44) and 27 days (range 18-51), respectively. After CR, five patients underwent allogeneic transplantation and 10 patients received a second course of FLAG-IDA. Ten out of 15 patients who achieved CR with FLAG-IDA relapsed at a median of 7.7 months (95% CI 1.8 to 13.6 months). Overall survival (OS) after FLAG-IDA in the surviving cohort had a median of 4 months. We found a significantly better OS in patients who received allogeneic transplantation post-FLAG-IDA than those who did not (median 11.4 months *vs.* 2.7 months; HR 0.29; 95% CI 0.1 to 0.6; p=0.017).** Conclusions: **In our series, FLAG-IDA demonstrated to be an effective salvage chemotherapy regimen, however, the benefit in survival of this rescue treatment was restrained to patients who underwent allogeneic transplantation.**

Key words: FLAG-IDA-leukemia-relapse-survival-transplantation

INTRODUCTION

Even though important advances in diagnosis and therapy of acute leukemia have been recently accomplished, most of the patients die of this disease.[1] Acute leukemia in adults and children includes a spectrum of diseases that ranges from patients with a very poor prognosis, like older patients with acute myeloid leukemia (AML) to those with childhood acute lymphoblastic leukemia (ALL), where the cure rate with chemotherapy approaches 85%[1, 2]. Patients with refractory or relapsed leukemia have a poorer outcome, and allogeneic hematopoietic stem cell transplantation (HSCT) is recommended in these patients, provided that complete remission (CR) is achieved previous to transplantation[1]. In these settings, FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin) has been indicated in both, adults and children with AML or ALL[2, 3]. FLAG-IDA is a combination chemotherapy based on the effect of priming with granulocyte colony-stimulating factor on blast cells, in order to increase their susceptibility to specific cell cycle agents, such as cytarabine[4]. The addition of fludarabine enhances the intracellular concentration of the cytarabine active metabolite, ARA-C-5´triphosphate, in leukemic blasts. Also, idarubicin is known to be less susceptible to multidrug resistance and may be less cardiotoxic.[3] We aimed to evaluate the chemo-

therapy regimen composed by fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) in patients with relapsed / refractory (R / R) acute leukemia (AL).

PATIENTS AND METHODS

In a non-randomized retrospective study, we evaluated 33 patients with R / R AL who underwent FLAG-IDA as rescue regimen: 17 (52%), 14 (42%) and 2 (6%) patients had myeloblastic, lymphoblastic and biphenotypic leukemia, respectively. The patients were treated in 3 different institutions between June 2001 and April 2007.

Cytogenetic studies at diagnosis were abnormal in 18 cases, normal in 10 cases and no metaphases were obtained in 5 cases. After diagnosis of AL, all patients had already received first line chemotherapy, according to the corresponding protocol of the Argentine Group for the Treatment of Acute Leukemia Study (GATLA). FLAG-IDA was indicated due to relapsed AL in 27 patients and refractory AL in 6 cases. Before administering FLAG-IDA, 17 (52%) patients were in their first relapse, 12 patients (36%) had received at least 2 different chemotherapy protocols (anti-CD33 monoclonal antibody combined with chemotherapy in 3 cases), and 4 (12%) patients underwent bone marrow transplantation (2 autologous transplantation and 2 allogeneic related transplantation). The median time from diagnosis of relapse or resistance to the beginning of FLAG-IDA was 10.23 months (r= 1.6 to 131 months).

The doses of FLAG-IDA were administered as follows: 30-minute intravenous infusion of fludarabine 25 mg / m^2 during days 1 to 4, 3-hour intravenous infusion of cytarabine 2 gr / m^2 during days 1 to 4 (starting 4 hours after the beginning of fluradarabine), 15-minute intravenous infusion of idarrubicine 12 mg / m^2 during days 1 to 3 after ending cytarabine, and subcutaneous G-CSF 5 mcg / Kg daily, since day 0 to the end of chemotherapy, and resuming 7 days after completing chemotherapy until granulocyte recovery[2, 3]. Routine procedures and preventive measures, such as antibiotic prophylaxis and treatment were chosen by each institution following international recommendations.

For each patient, we registered data related to: age, type of leukemia, performance status, karyotype at diagnosis, laboratory analysis, response category, consolidation treatment after FLAG-IDA, date of relapse and last visit or death. Toxicity of FLAG-IDA was evaluated according to NCI 3.0 version. Institutional Ethics Committees approved the study.

Complete remission (CR) and other response categories were defined as previously described[1, 5]. Overall survival (OS) was calculated from beginning of FLAG-IDA until death from any cause or date of last visit. Relapse free survival (RFS) was defined for patients in CR from date of attaining CR until AL relapse or death from any cause[5]. Time-event variables were estimated by the Kaplan-Meier method and compared with log-rank test. Multivariate analysis was performed with Cox-regression analysis. All *p* values were two sided and $p < 0.05$ was considered statistically significant.

RESULTS

At the start of the FLAG-IDA protocol median age was 22 years (r= 11-56) and performance status was: 0 (n= 11), 1 (n= 13) and ≥ 2 (n= 9). None of the patients had compromise of the central nervous system. At day 0, media values of hemogram were: WBC 25,257.57 / mm^3 (±52,772.80); percentage of blast cells in peripheral blood 40.76% (±37.99); haemoglobin (Hb) 9.34 gr / dL (±2.22); and platelet count 89,284 / mm^3 (±11, 4910.26). All patients had at least 1 episode of febrile neutropenia in a median of 8 days (r= 3-17) with positive blood cultures in 42% of the events. Grade 5 toxicity occurred in 7 patients resulting in a treatment-related mortality of 21.1%. All the deaths were due to sepsis. In patients with hematological recovery (n= 21; 63.6%) the median time to neutrophil recovery (> 0.5 x 10^9 / L) was 24 days (r= 10-38); platelet counts of more than 20 x 10^9 / L and 50 x 10^9 / L were reached in a median time of 24 (r= 17-44) and 27 days (r= 18-51), respectively. Median hospitalization time was 28 days (r= 1-86).

Overall, CR was achieved in 15 patients (45.5%), partial remission (PR) in 1 patient (3%) and 10 patients presented disease progression (30.3%). Response rates according to AL category are shown in Table I. In the univariate analysis, factors significantly associated with CR were haemoglobin level (10.2 gr /

TABLE I. Complete Remission Rate related with FLAG-IDA treatment (n= 33)*

Variable	Number of Patients	CR rate (%)
All patients	33	15 45.4)
Relapsed AL	26	12 (46.1)
Refractory AL	7	3 (42.8)
Myeloid AL	17	5 (29.4)
Lymphoid AL	14	8 (57.1)
Biphenotypic AL	2	2 (100)

* AL= acute leukemia; CR= complete remission.

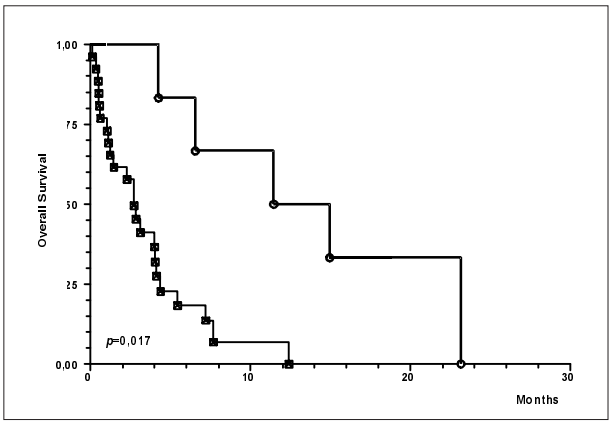

Fig. 1. Overall survival (OS) of patients who underwent allogeneic HSCT post-FLAG-IDA (thick line) compared to those who did not (thin line).

dL *vs.* 8.6 gr / dL; *p*= 0.04) and percentage of blast cells in peripheral blood (29.6% *vs.* 56.1%; *p*= 0.05) at the beginning of FLAG-IDA. After CR, 5 patients underwent HSCT (HLA-matched related donor in 4 patients and unmatched related donor in 1 patient) and 10 patients received a second course of FLAG-IDA (2 of these patients underwent allogeneic transplantation from HLA-matched unrelated donor and 8 without consolidation with transplantation). No grade 4 or 5 toxicity occurred with the second course of FLAG-IDA. Ten out of 15 patients in CR relapsed with a RFS of 7.7 months (r= 1.8-13.6).

OS after FLAG-IDA in the surviving cohort had a median time of 4 months (95% CI, 2.4 to 5.6 months) and 1-year survival was 12.33%. We found a significantly better OS in patients who underwent allogeneic HSCT post-FLAG-IDA compared to those who did not (median 11.4 vs. 2.7 months; HR 0.29; 95% CI, 0.1 to 0.6; *p*= 0.017) (Fig. 1); in patients with normal karyotype at diagnosis of AL: 14.9 *vs.* 3.1 months; HR 0.35 (95% CI, 0.1 to 0.8; *p*= 0.011); and in patients with Hb level ≥10 gr / dL previous FLAG-IDA: 7.2 *vs.* 2.7 months; HR 0.39 (0.19 to 0.82; *p*= 0.0197). In the multivariate analysis, only those who had received allogeneic transplantation post-FLAG-IDA, remained statistically significant for OS (Fig. 1).

DISCUSSION

We have analysed the outcome of FLAG-IDA in a heavily pre-treated series of patients with R / R AL, both AML and ALL. Results on the use of G-CSF as priming in AL chemotherapy have been discordant in comparative studies. Estey et al. reported not differences between patients with myeloid malignancies receiving G-CSF or not, regarding CR or OS, with a combination of fludarabine and cytarabine[6]. Löwenberg et al. found a higher CR and OS in the subgroup of standard risk AML[7]. We found a 45.4% of CR following a single course of FLAG-IDA. Trials evaluating FLAG-IDA in patients with refractory / relapse AML have reported a response rate of CR between 40 and 60%. The highest CR rate has been reported in children with AML. Few reports have evaluated the efficacy of FLAG-IDA in patients with ALL. A CR rate of 39% has been reported, but none of the patients with refractory disease achieved CR in this series[8]. However, G-CSF had been administered after completing chemotherapy and the priming effect of G-CSF may have been lost[8]. Effects of growth factors priming have been studied both in AML cells and in ALL[4, 9], and response may be higher in ALL with myeloid antigen co-expression[9]. We reported a higher response rate in ALL patients including 2 patients previously refractory to induction chemotherapy. However, in patients with Phi+ALL, we had a lower CR rate (1 / 3) compared to other authors (5 / 6), and the only patient who responded received imatinib along with FLAG-IDA[10]. Toxicity observed in our series and in previous studies was considerable, probably because patients with high risk factors were included[11]. Mortality rate with FLAG-IDA may be clearly superior in patients with refractory / relapsed disease, compared to those with de novo disease, and 0% mortality has been reported when FLAG-IDA was used as first-line therapy[3]. On the other hand, no treatment-related mortality was observed during a second course of FLAG-IDA in this and other series[8], even though higher mortality in children has been described because of a more prolonged myelosuppression[2]. We did not evaluate minimal residual disease after induction with FLAG-IDA, which indicates the quality of the response and is a prognostic marker in the upfront treatment[1]. However, minimal residual disease has not been evaluated in the setting of relapsed disease and the optimal timing has not been established[12].

In our series, FLAG-IDA demonstrated to be an effective salvage chemotherapy regimen but presented a high rate of treatment-related deaths. We found that the benefits of this rescue treatment on survival were restrained to patients subsequently who underwent allogeneic transplantation, underlying the correct selection of patients when an effective but toxic treatment was indicated. New agents in this setting should be considered.

RESUMEN

Objetivo: Evaluar la respuesta al esquema FLAG-IDA (fludarabina, citarabina, idarrubicina y G-CSF) en pacientes

con leucemia aguda (LA) recaída/refractaria (R/R). **Métodos:** Estudio retrospectivo multicéntrico. Treinta y tres pacientes con LA R/R: mieloblástica 17 (52%), linfoblástica 14 (42%) y bifenotípica 2 (6%). **Resultados:** 15 (45.5%) pacientes obtuvieron remisión completa (RC) y 7 pacientes fallecieron resultando en una mortalidad del 21,1%. En pacientes con recuperación hematológica la mediana para alcanzar > 0.5 x 10^9/l neutrófilos fue de 24 días (rango 10-38) y la recuperación de plaquetas de >20 x 10^9/l y > 50 x 10^9/l fue de 24 días (17-44) y 27 días (18-51), respectivamente. Posterior a la RC, 7 pacientes recibieron trasplante alogénico (TxMO) y 10 pacientes un segundo ciclo de FLAG-IDA. 10/15 pacientes en RC presentaron recaída en una mediana de 7,7 meses (95% IC 1,8 a 13,6). La mediana de sobrevida global (SG) pos-FLAG-IDA fue de 4 meses. Hubo una diferencia significativa en SG a favor de los pacientes que recibieron TxMO pos-FLAG-IDA (11,4 *vs* 2,7 meses; HR 0,29; 95% IC 0,1 a 0,6; p= 0,017). En el análisis multivariado, el TxMO pos-FLAG-IDA retuvo significancia estadística. **Conclusiones**: El esquema FLAG-IDA demostró ser efectivo para obtener RC, independiente del tipo de LA y aún en pacientes refractarios. Sin embargo, el beneficio en SG está influenciado por el tratamiento posterior con TxMO.

Palabras Claves: FLAG-IDA-leucemia-recaída-sobrevida-trasplante

REFERENCES

1. Appelbaum FR, Rosenblum D, Arceci RJ, et al. End points to establish the efficacy of new agents in the treatment of acute leukemia. **Blood** 2007; 109: 1810-1816.
2. Fleischhack G, Hasan C, Graf N, Mann G, Bode U. FLAG-IDA (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experiences of a phase II trial. **Br J Haematol** 1998; 102: 647-55.
3. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. **Br J Haematol** 1997; 99: 939-44.
4. Tosi P, Visani G, Ottaviani E, Manfori S, Zinzani PL, Tura S. Fludarabine + Ara-C + G-CSF: cytotoxic effect and induction of apoptosis on fresh acute myeloid leukemia cells. **Leukemia** 1994; 8: 2076-2082.
5. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. **J Clin Oncol** 2003; 21: 4642-4649.
6. Estey E, Thall P, Andreeff M, et al. Use of granulocyte colony-stimulating factor before, during, and after fludarabine plus cytarabine induction therapy of newly diagnosed acute myelogenous leukemia or myelodysplastic syndromes: comparison with fludarabine plus cytarabine without granulocyte colony-stimulating factor. **J Clin Oncol** 1994; 12: 671-8.
7. Löwenberg B, van Putten W, Theobald M, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. **New Engl J Med** 2003; 349: 743-52.
8. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. **Ann Hematol** 2005; 84: 792-5.
9. Visani G, Tosi P, Zinzani PL, et al. FLAG (fludarabine, cytarabine, G-CSF) as a second line therapy for acute lymphoblastic leukemia with myeloid antigen expression: in vitro and in vivo effects. **Eur J Haematol** 1996; 56: 308-12.
10. Virchis A, Koh M, Rankin P, et al. Fludarabine, cytosine arabinoside, granulocyte-colony stimulating factor with or without idarubicin in the treatment of high risk acute leukaemia or myelodysplastic syndromes. **Br J Haematol** 2004; 124: 26-32.
11. Deane M, Koh M, Foroni L, et al. FLAG-idarubicin and allogeneic stem cell transplantation for Ph-positive ALL beyond first remission. **Bone Marrow Transplant** 1998; 22: 1137-43.
12. Davis BH, Holden JT, Bene MC, et al. 2006 Bethesda International Consensus recommendations on the flow cytometric analysis of hematolymphoid neoplasia: medical indications. **Cytometry B Clin Cytom** 2007; 72 Suppl 1: S5-13.