Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Special Article - Acute and Chronic Myeloid Leukemia

Fludarabine, Cytarabine and Gentuzumab Ozogamicin (FLA-GO) as Salvage Therapy and Bridge to Transplant in Adult Relapsed Acute Myeloid Leukemia (AML) Patients

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Received: January 25, 2017; **Accepted:** March 16, 2017; **Published:** March 31, 2017

Abstract

Twenty-seven patients affected by relapsed/refractory acute myeloid leukemia (AML) were treated with a combination of fludarabine, cytarabine; (FLA) and gentuzumabozogamicin(GO). Complete remission (CR) rate was 37% (10/27 patients), with one patient (4%) dying early because of treatment related infection. Six out of 10 patients (60%) who achieved a second CR were able to receive allogeneic SCT. Although the difference was not statistically significant, likely due to the small sample size, we observed that CR rate was higher in patients< 60 years and with a first CR duration >12 months. Two-years cumulative incidence of relapse and overall survival were 20±13% and 20±8%, respectively. In conclusion, although based on a small sample size, our study suggests that the association of FLA plus GO has a favorable toxicity profile and might be used as a bridge to transplant in young patients, especially when the duration of first CR is ≥ 12 months.

Keywords: Acute myeloid leukemia, Gentuzumabozogamicin, CD33 antigen, Salvage therapy

Introduction

Prognosis of adult patients with relapsed/refractory acute myeloid leukemia (AML) is generally unsatisfactory with a 5-year overall survival (OS) of 10-30% [1-4]. Such a dismal outcome is well explained with a lack in availability of effective salvage options and with the problematic access to allogeneic stem cell transplantation (ASCT), which remains the only potential curative approach.

Salvage regimens generally rely on the delivery of high-dose cytarabine (ARA-C), alone or in combination, followed by ASCT [5]. Among combinatorial approaches, the association of fludarabine and ARA-C (FLA) was found to be superior to ARA-C single agent. In fact, fludarabine modulates the pharmacologic activation of ARA-C [6-8] therefore increasing the rate of accumulation of its active metabolite ARA-C 5'-triphosphate [6].

Besides attempts to ameliorate the efficacy of conventional chemotherapy, developing and implementing programs of "targeted therapy" has represented a further expedient to approach difficult-to-treat diseases such as relapsed/refractory AML. Among agents able to target specific leukemic antigens or pathways, Gentuzumab Ozogamicin (GO) is one of the most extensively investigated. GO is a humanized anti-CD33 monoclonal antibody conjugated to a semisynthetic derivative of calicheamicin, a cytotoxic drug that is released inside the leukemic cells after the internalization of the immunoconjugate. CD33 is a 67-kD transmembrane cell surface glycoprotein receptor, which represents an attractive target for immunotherapy since it is expressed on the external surface of leukemic blasts in more than 80% of patients with AML, but not on normal precursor hematopoietic cells [4]. Either as a single agent or in combination with chemotherapy, GO was reported to improve overall responses rate in adults with relapsed/refractory AMLs [8-10].

Based on these premises, we conducted a retrospective analysis of 27 adult patients with relapsed/refractory AML, to evaluate the efficacy and the safety of the association FLA plus GO (FLA-GO) and to assess the feasibility of ASCT after FLA-GO.

Patients and Methods

Patients

Twenty-seven adult patients with refractory/relapsed AML treated with FLA-GO regimen between 2006 and 2010 at the Policlinico Tor Vergata of Rome, were analyzed for the purposes of the present study. Approval for this study was obtained from the institutional review board. All patients received written informed consent in accordance with the declaration of Helsinki. Inclusion criteria were relapsed/refractory AML, age >18 years, ECOG performance status≤ 2 [11], normal renal and liver function (creatinine ≤ 2 mg/dl, total bilirubin ≤ 2 mg/dl), adequate cardiac function (LVFE ≥50%). Patients with Acute Promyelocitic Leukemia were excluded.

Routine molecular, karyotypic and immunophenotypic analysis

Total RNA was extracted from Ficoll-Hypaque isolated bone marrow mononuclear cells collected both at diagnosis and at disease

Citation: Cefalo M, Del Principe MI, Buccisano F, Di Piazza F, Ottaviani L, Maurillo L, et al. Fludarabine, Cytarabine and Gentuzumab Ozogamicin (FLA-GO) as Salvage Therapy and Bridge to Transplant in Adult Relapsed Acute Myeloid Leukemia (AML) Patients. Ann Hematol Oncol. 2017; 4(4): 1145.

relapse using standard procedures [12] and reverse-transcribed with random hexamers as primers [13]. Diagnostic molecular studies for recurrent translocations were performed according to previously published methods [13]. DNA was also extracted using a column-based Qiagen kit protocol. Fms-like tyrosine kinase- internal tandem duplication (FLT3 ITD) and nucleophosmin1 (NPM1) gene mutations were investigated using protocols reported elsewhere [14-17].

Conventional karyotyping was performed on bone marrow aspirates after short-term culture and analysed after G-banding. The description of the karyotype was according to the International System for Human Cytogenetic Nomenclature [18].

Bone marrow samples were also collected for immunophenotyping with a standard panel of antibodies [19]. Briefly, each antibody was incubated with 1-2x10^6 cells in a 100µl of volume, and isotype-matched antibodies were used as negative controls. After incubation, cells were re-suspended in 0.5 ml PBS and analyzed with a flow cytometer (Facs Canto; Becton Dickinson). Percentage of CD33 positive blasts was determined drawing a proper gate on the leukemic population in the FSC/SSC plot.

Treatment schedule

The chemotherapy regimen consisted in a 30-minute infusion of intravenous fludarabine, 30 mg/m^2/day on days 1-5 and, on the same days, in 2-hour infusion of intravenous ARA-C, 2 g/m^2/day. In order to generate the best pharmacologic interaction between fludarabine and ARA-C, infusion of ARA-C began 4 hours after the end of that of fludarabine. On day 6, intravenous GO (Mylotarg, Pfizer, New York, NY, and Ben Venue Laboratories, Bedford, OH, USA) was infused at the dose of 6 mg/m^2 Thirty minutes before GO administration, all patients received a pre-medication with methylprednisolone (40 mg, flat dose). Duration of GO infusion was two hours. All patients had a central venous catheter (CVC) inserted, all received fluoroquinolone-based and anti-fungal prophylaxis from the start of chemotherapy until resolution of neutropenia or introduction of empirical antibiotic therapy for febrile neutropenia. When transfusions were required, blood components were irradiated before infusion [20].

Response definition and safety monitoring

Bone marrow aspiration for determination of response was performed on day + 28±2 from the start of chemotherapy. Response criteria were those of the International Working Group [21] based on whichCR was defined as a bone marrow blasts count <5%, absolute neutrophil count >1x10^9/l, platelets count >100x10^9/l and transfusions independence. Partial Remission (PR) was defined as a bone marrow blasts percentage of 5% to 25%. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events [22]. Early death (ED) was defined as death within 31 days following day 1 of chemotherapy administration.

Outcome definition and statistical analysis

Descriptive statistics are presented including median and range for continuous variables, absolute and relative frequencies for categorical variables. The relapse rate after FLA-GO was assessed by the cumulative incidence (CI) function, using the competing risks method and considering death without relapse like competing event. The Kaplan-Meier product-limit method was used to estimate and plot the OS. Differences between groups were determined using the Gray's test and the log-rank test for the CI measures and for OS, respectively. A p value of <0.05 was considered statistically significant. All the analysis were conducted using software R version 2.15.0.

Table 1: Patient's characteristic.

PatientsCharacteristic	n(%)
Total patients	**27**
Gender	
Male	20 (74%)
Female	7 (26%)
Age, medianyears	58
Range	22-71
≥60 years	12(44%)
<60 years	15(56%)
PS ECOG	
0	8(30%)
1	16(59%)
2	3(11%)
WBC count	
≥50x10^3/L	6(22%)
<50x103/L	21(78%)
Diseasephase	
Relapsed	22(81%)
Refractory	5(19%)
Cytogeneticriskgroups	
Good	2(8%)
Intermediate	15(55%)
Poor	8(29%)
Unknown	2(8%)
CD33 expression	
≥80%	19(70%)
<80%	8(30%)
NPM1	
Positive	3(11%)
Negative	16(60%)
Unknown	8(29%)
FLT3	
Positive	8(30%)
Negative	8(30%)
Unknown	11(40%)
Blastcount	
>50%	15(58%)
<50%	11(42%)

Results

The clinical and biological characteristics of the 27 patients are summarized in Table 1. Twenty patients were males, 7 females. Median age was 58 years (range 22-71 years). Five patients had

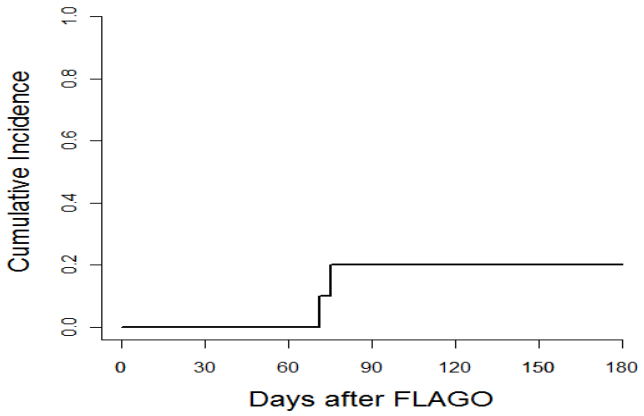

Figure 1: Cumulative Incidence of Relapse after FLAGO 20±13%.

an AML primarily refractory to a first induction course and 22 were in first relapse after a frontline induction regimen combining anthracycline, etoposide and ARA-C. Among patients in first relapse, 2 relapsed after ASCT and 1 after autologous SCT. In 14 of 22 (64%) patients who relapsed, duration of first CR (CR1) was ≥12 months. Overall, median duration of CR1 was 9 months (range 2-110). At the time of resistance or relapse, cytogenetic data were available in 25 of 27 (93%) patients: 2 (8%), 15 (55%) and 8 (29%) had a favorable-, intermediate- and unfavorable-risk karyotype, respectively [23]. From a molecular point of view, 8 of the 27 (30%) patients had FLT3 ITD mutation and 3 (11%) had both NPM1 and FLT3-ITD mutation. Median percentage of CD33 expression was 88% (range 4-100%) with 19 patients (70%) showing positivity in more than 80% of the leukemic blasts.

The overall CR rate after 1 course of FLA-GO was 37% (10/27 patients). The median time to CR was 36 days (range 25-49) with no PR being observed. None of the patients affected by primary refractory AML achieved a CR after FLA-GO. Patients younger <60 years and with CR1 duration >12 months achieved CR more frequently than those of age>60 years (70% *vs.* 30%, p=ns) or with CR1 <12 months ((70% vs 30%, p=ns). No difference in CR rate was observed according to CD33 expression or cytogenetic pattern. Six out of 10 patients (60%) (median age 55, range 27-63) who achieved a CR2 were successfully addressed to ASCT, with none of them receivingpre-emptive or prophylactic donor lymphocyte infusion. With a median follow-up of 5.3 years, the6-months cumulative

Table 2: Side effects.

Adverse events	Patients n(%)
	27
Febrile neutropenia	**22**
Grade III	21 (78%)
Grade V	1 (3.7%)
Pneumonitis	10
Grade II	7(26%)
Grade III	3(11%)
Mucositis	**6**
Grade III	6(22%)
Livertoxicity	**2**
Grade II	2(7%)
Thrombosis Central venouscatheter	**2**
Grade II	2(7%)
Bleeding	**6**
Grade II	3(11%)
Grade IV	3(11%)

incidence of relapse (CIR) and 2-yearsOS was 20±13% (Figure 1) and 20±8% (Figure 2), respectively.

All patients experienced grade 3-4 chemotherapy-related hematological toxicities. The median duration of neutropenia and thrombocytopenia was 27 (range 11-33) and 25 days (range 9-30), respectively. Febrile neutropenia was observed in 78% of the patients whereas infectious episodes (pneumonia)in 37% [22]. One case of febrile neutropenia was fatal (grade 5) (ED=3.7%). Grade 3 mucositis was observed in 6 patients (22%) and in 2 (7%) a mild and transient liver toxicity. No infusion related symptoms or sinusoidal obstructive syndrome (SOS) due to GO administration was reported (Table 2), even in patients who received to ASCT.

Discussion

We evaluated the efficacy and safety of a combined immune-chemotherapy regimen associating fludarabine, ARA-C and GO, in a group of patients affected by relapsed or primary refractory AML. Therapy was well tolerated and CR was reported in 37% of those with relapsed AML. This figure is in line with other purine nucleoside analog-based regimens such as FLA (36%) [7], FLAG-

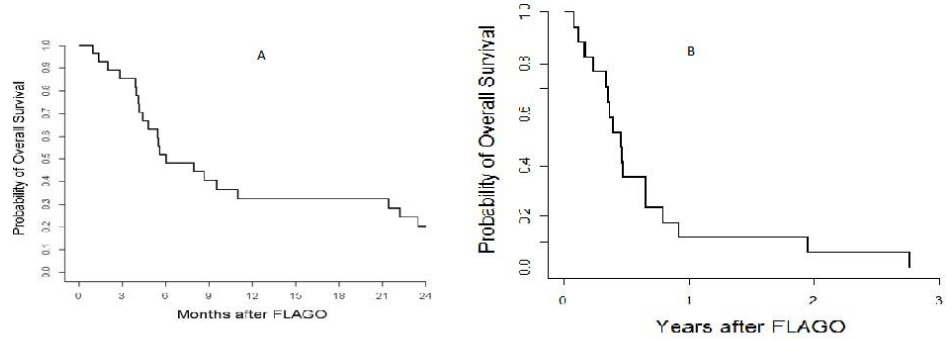

Figure 2: Kaplan-Mejer estimate of Overall Survival (OS) of responders patients (A) and of non-responders patients (B).

IM (fludarabine, ARA-C, idarubicin, GO) (39%) [24] or clofarabine (32%) [25]. In a recent report, the CR rate of 259 patients treated with FLA-idarubicin or FLAGO-idarubicin was 51%. Therefore in large series, it appears that the addition of an anthracycline may increase the effectiveness of GO [26].

No patients with primary refractory AML achieved response after FLA-GO regimen. Probably, this very high risk group of patients would benefit from the use of GO within anthracycline-based regimens or newer therapies.

A successful outcome after salvage therapy depends on duration of first CR, cytogenetics at diagnosis and previous history of ASCT [8-9,25-27]. Although the difference was not statistically significant, likely due to the small sample size, we observed that patients younger than 60 years and those with CR1 duration ≥12 months had a higher response rate.

As regard to the impact of genetics/cytogenetics on response rate, we were not able to appreciate any significant difference between the risk-categories, likely due to the small sample size. Furthermore, only one instance of favorable karyotype was detected with the majority of subjects belonging to the intermediate- or unfavorable-risk category.

Preclinical data indicate that GO is more effective in AMLs with a high CD33 expression [28]. In a study of GO single-agent for unfit elderly patients with previously untreated AML, Amadori et al. confirmed this observation [29]. In our study no association between CD33 expression and clinical outcome emerged, this is in line with others' experience in which GO wasnot delivered as single agent but rather given in association with chemotherapy [30,3 1].

We reported a manageable hematologic toxicity, comparable to that commonly described in the setting of salvage therapy [7,32] and inferior to the one observed in the recent series of 259 patients treated with GO in the context of an anthracycline-based regimen [26]. Even liver toxicity was negligible and no instances of SOS were observed in the overall population and in patients submitted to ASCT [31,33-36]. Overall, ED rate was in line or even lower than what observed in other chemotherapy trials [8,25]. The optimal schedule of GO administration remains uncertain [37]. In most clinical trials the first dose of GO was administered on day 1 together with chemotherapy [31,38]. Others opted for a delayed administration so that GO was infused on the last day of chemotherapy [24,32,37,39]. The combination of methylprednisolone pre-medication and delayed GO infusion might explain why no serious infusion related adverse events were observed. Additionally, the delayed GO infusion might be particularly indicated in patients with high WBCc. In fact, the fall in the number of WBC induced by chemotherapy may prevent either a GO-induced tumor lysis syndrome or the so called "sink-effect" due to the peripheral blast absorption of anti-CD33 [37]. Relapsed/refractory AML is a fatal condition that cannot be cured by therapy other than ASCT [40]. However, less than 30-40% of the candidates has eventually access to the procedure because of the very short duration of CR2, the prolonged cytopenia and, more in general, because of the toxicity caused by the multiple exposures to chemotherapy [41,42]. In our series, 60% of the patients achieved a CR2 that was stable enough to allow an ASCT to be performed. This results are in line with other studies [32,38] and similar to those of clofarabine containing protocols.

Although based on a small sample size, our results suggest that this combination can generate promising response rates in a population of very high-risk AML patients, younger than 60 years and with a CR1 duration ≥12 months, without relevant therapy-related toxicities. Further studies are needed to confirm our results and to better define the subsets of patients who may benefit from this combinatorial therapy. The FLA-GO regimen may also represent an advantageous preparatory salvage for candidates to receive ASCT as a post-CR2 consolidation, mainly for its favorable toxicity profile.

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Ann Hematol Oncol - Volume 4 Issue 4 - 2017
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Cefalo M, Del Principe MI, Buccisano F, Di Piazza F, Ottaviani L, Maurillo L, et al. Fludarabine, Cytarabine and Gentuzumab Ozogamicin (FLA-GO) as Salvage Therapy and Bridge to Transplant in Adult Relapsed Acute Myeloid Leukemia (AML) Patients. Ann Hematol Oncol. 2017; 4(4): 1145.