Ann Hematol (1999) 78:380–384

ORIGINAL ARTICLE

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Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of acute myeloid leukemia relapsing after autologous stem cell transplantation

Received: October 19, 1998 / Accepted: March 30, 1999

Abstract Twenty-six patients affected by acute myeloid leukemia (AML) who relapsed after autologous stem cell transplantation (ASCT) were treated with the FLAG regimen (fludarabine, cytarabine, and G-CSF). Their median age was 39 years (range 14–59). The median interval from achievement of CR to ASCT was 4 months (2–8). The conditioning regimen was BAVC (BCNU, amsacrine, VP-16, cytarabine) in eight patients, BuCy (busulfan, cyclophosphamide) in 13, and TBI-Cy (total body irradiation, cyclophosphamide) in five. Relapse occurred after a median of 7 months (2–18). ASCT had been performed in CR1 for 23 patients and in CR2 for three. Nineteen patients had been given bone marrow, seven peripheral blood stem cells collected following consolidation plus G-CSF. Overall, CR was obtained by 13 patients (50%), all remitters requiring a single course. The median time for hematological recovery of neutrophils >500/μl and platelets >20,000/μl was 24 and 30 days, respectively. The median duration of G-CSF administration was 25 days, while the median hospitalization was 31 days. There were four deaths in induction (15%), while nine patients (35%) were resistant. After achieving CR, two patients received allogeneic BMT, five a second ASCT, and four were consolidated with HD-ARA-C. Only two patients were judged unable to receive any further therapy. There were 14 documented infections, while nine patients experienced fever of unknown origin. WHO >2 nonhematological toxicity consisted of stomatitis (50%), hepatic dysfunction (11%), diarrhea (11%), and lethargy (4%). Median overall survival and disease-free survival were 6 and 13 months, respectively. Six patients are in CCR at present. We conclude that FLAG is effective in patients with AML who are relapsing after ASCT. The toxicity is acceptable, enabling most patients to receive further treatment, including second transplantation procedures.

Key words Acute myeloid leukemia · Autologous stem cell transplantation · Relapse

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Introduction

Autologous stem cell transplantation (ASCT) is being used increasingly for post-remission treatment of acute myeloid leukemia (AML) [13–15]. For adult patients autografted in first complete remission (CR), reported leukemia-free survival ranges from 30 to 50%, leukemic relapse remaining the major reason for treatment failure [14]. The prognosis of patients relapsing from ASCT is usually poor [4, 6, 19]; however, the achievement of a second CR may offer a chance of further transplantation, aimed at prolonged disease-free (DFS) and overall survival (OS).

High or intermediate-dose arabinosylcytosine (ARA-C), alone or in combination, has been reported effective in the salvage treatment of AML [1, 16, 17]. The clinical efficacy of this approach depends on the higher intracellular concentration of the active metabolite ara-C 5' triphosphate (ARA-CTP). Gandhi et al. demonstrated that the combination of fludarabine

(FAMP) and ARA-C results in a relevant increase of intracellular retention of ARA-CTP [12]. On the other hand, in vitro studies have shown that hematopoietic growth factors (HGFs) may render previously dormant leukemic cells more sensitive to cytotoxic drugs via a mechanism of cycling [27, 28, 34]. In addition, HGFs significantly enhance ARA-C incorporation into DNA, irrespective of the number of cells in S-phase [30].

Based on the above observations, Estey and coworkers developed a chemotherapy program called FLAG, including FAMP, ARA-C, and G-CSF, which is reported to be as effective and well tolerated in newly diagnosed patients as it is in resistant or relapsing patients with AML [9, 10]. The efficacy and tolerability of the FLAG regimen has been confirmed in a number of subsequent studies including poor-risk AML patients treated with FLAG or with FLAG plus either idarubicin or mitoxantrone [5, 11, 18, 23–26, 35]. We report here the disease characteristics and treatment results from a series of 26 patients affected by AML who relapsed following ASCT and were treated with the FLAG program.

Material and methods

Between March 1996 and March 1998, after we had obtained their informed consent, 26 eligible patients received the FLAG protocol. As shown in Table 1, all patients had AML and were relapsing after ASCT, which had been performed during CR1 in 23 patients (88%) and during CR2 in three (12%). Diagnosis had been made according to FAB criteria [2]. There were 14 men and 12 women with a median age of 39 years (range 14–59). All patients had received the induction regimen of the current GIMEMA/EORTC AML10 clinical trial, which consists of a 3+5+10 randomized schedule containing idarubicin (10 mg/m^2 on days 1, 3, 5) or daunorubicin (50 mg/m^2 on days 1, 3, 5) or mitoxantrone (10 mg/m^2 on days 1, 3, 5), plus ARA-C (100 mg/m^2 as continuous i.v. infusion days 1–10), plus etoposide (100 mg/m^2 days 1–5). Consolidation included intermediate-dose ARA-C plus the same anthracyclines used in induction. The median interval between achievement of CR and ASCT was 4 months (range 2–8). Nineteen patients underwent transplantation with bone marrow, while seven received peripheral blood stem cells collected following consolidation plus G-CSF. The conditioning regimen was BCNU, amsacrine, VP-16, cytarabine (BAVC) [21] in eight patients, busulfan and cyclophosphamide (BuCy) [33] in 13, and total body irradiation plus cyclophosphamide (TBI-Cy) in five. All patients received unpurged stem cells. Relapse occurred after a median of 7 months (range 2–18); it is worthy of note that 24 of the 26 patients (92%) relapsed within 1 year. Performance status (PS) was assessed according to WHO criteria: nine patients were in PS 0, 11 in PS 1, five in PS 2, and one was in PS 3.

In order to be included in the FLAG program, patients had to present with a serum bilirubin level less than 2 mg/dl, creatinine less than 2 mg/dl, no evidence of cardiac dysfunction, and a PS between 0 and 3. CR was defined as less than 5% of blasts in a normocellular or hypercellular bone marrow with normal peripheral and differential counts in the absence of extramedullary leukemia lasting at least 2 months. Resistance was recorded either as treatment failing to induce significant bone marrow hypoplasia in patients surviving 15 days at least, or as leukemic regrowth following the hypocellular phase [8]. Median number of days to hematological recovery was calculated by the product-limiting method of Kaplan and Meier [20]. Side effects were assessed according to WHO criteria. OS was calculated from the date when FLAG treatment began, DFS from achievement of CR to relapse; patients who died in CR were plotted as censored. Survival curves were obtained by the Kaplan-Meier method [20]. Patients achieving CR received a second identical consolidation treatment, followed by an individualized program of post-remission therapy, depending mainly upon age and clinical status.

Patients were treated with FAMP 30 mg/m^2 administered i.v. at the same time daily for 5 consecutive days over 0.5 h. Three and a half hours after the completion of each daily fludarabine infusion, 2 g/m^2 ARA-C was administered i.v. over 4 h. Recombinant human G-CSF (filgrastim or lenograstim) was administered at a dose of 5 μg/kg from day 0 (24 h before starting chemotherapy) to polymorphonuclear recovery (more than 0.5×10^9/l). An additional cycle was programmed in case of partial remission. As compared with the M.D. Anderson original schedule, a lower dose of G-CSF (i.e., 5 μg/kg vs. 400 μg/m^2) was employed in the present study.

Table 1 Characteristics of the 26 patients

Age in years (range)	39 (14–59)
Sex (M/F)	14/12
WHO performance status: *n* (%)	
0	9 (35)
1	11 (42)
2	5 (19)
3	1 (4)
Autografted in CR1, *n* (%)	23 (88)
Autografted in CR2, *n* (%)	3 (12)
Median interval between achievement of CR and ASCT, months (range)	4 (2–8)
Median interval between ASCT and relapse, months (range)	7 (2–18)
Conditioning regimen:	
BAVC	8
BuCy	13
TBI-Cy	5

Results

Therapeutic results are summarized in Table 2. Of the 26 patients accrued, all received the 5 days of chemotherapy. The overall CR rate was 50% (13 of 26), all remitters requiring a single course of chemotherapy. There were four deaths in induction (15%), three due to infections and one to cerebral hemorrhage. Nine patients (35%) were resistant to FLAG. As concerns resistant patients, 11 had a phase of bone marrow hypocellularity followed by leukemic regrowth, while in two of them chemotherapy failed to induce bone marrow aplasia. All patients experienced profound granulocy-

Table 2 Therapeutic response to FLAG and hematological toxicity

CR, *n* (%)	13/26 (50)
Primary resistant, *n* (%)	9/26 (35)
Induction death, *n* (%)	4/26 (15)
Median days to PMN >500 (range)	24 (13–28)
Median days to platelets >20,000 (range)	30 (22–79)
Median days of G-CSF administration (range)	25 (14–55)
Packed red cells units, median (range)	10 (4–25)
Platelet units, median (range)	12 (3–24)
Median days of hospitalization	31 (17–61)

Table 3 Nonhematological toxicity (WHO >2)

Type of toxicity	No. of patients (%)
Documented infections:	14 (54)
Bacterial	10 (38)
Fungal	4 (12)
FUO	9 (35)
Mucositis	13 (50)
Diarrhea	3 (11)
Hepatic	3 (11)
Neurological (lethargy)	1 (4)

topenia (less than 200/μl); the median time to reach PMN >500/μl and >1000/μl was 24 days (range 13–38) and 27 days (range 15–42), respectively. Thirty (range 22–79) and 34 (range 24–112) days was the median time to achieve platelet levels >20,000/μl and >100,000/μl, respectively. Hematological recovery was calculated taking into account all patients in whom neutrophils and platelets recovered to the above values. In remitters, the median duration of G-CSF administration was 25 days (range 14–55). The median period of hospitalization was 31 days (range 17–61). Supportive treatment consisted of a median of 10 packed red cell units (range 4–25) and 12 platelet units (3–24). In 23 of 26 patients (88%) fever occurred during the period of neutropenia secondary to chemotherapy exposure, and in nine cases there was fever of unknown origin (FUO). There were 14 documented infections, ten bacterial and four fungal, as detailed in Table 3. The median number of days with febrile neutropenia was 9; three patients had no fever at all. The nonhematological toxicity was acceptable. The most common side effects were mucositis (13/26, or 50%), increase of liver enzymes or serum bilirubin (3/26, or 11%), and diarrhea (3/26, or 11%). One patient experienced severe neurological toxicity (lethargy), which resolved spontaneously (Table 3). There were no differences in CR rates and toxicity according to the conditioning regimen of the original transplantation.

After achieving CR, five patients received second ASCT (four with bone marrow and one from peripheral blood stem cells), two a BMT from a matched, unrelated donor, and four were consolidated with HD-ARA-C. Only two patients were judged as being unable to receive any further therapy. Median survival of the whole patient population was 6 months (Fig. 1), while the DFS was 13 months (Fig. 2). Overall, six patients (three after ASCT, one after BMT, and two after HD-ARA-C) are at present in continuous CR after a median follow-up of 12 months. One patient died of severe chronic graft-versus-host disease following BMT while in first CR.

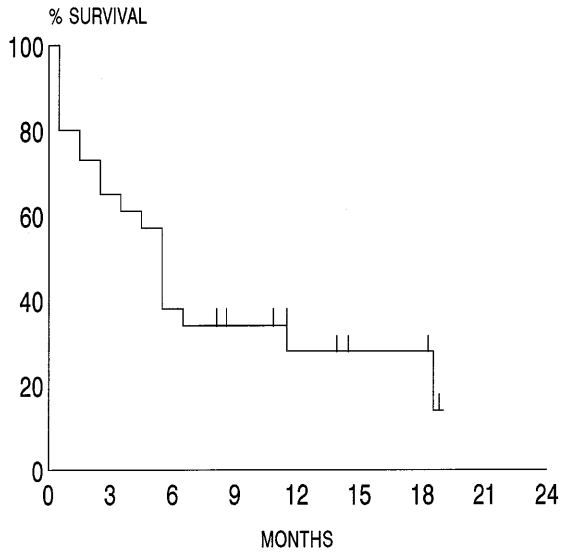

Fig. 1 Overall survival of the whole patient population

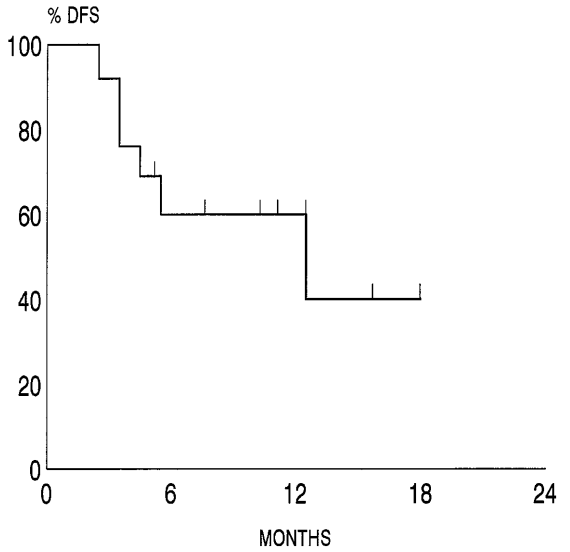

Fig. 2 Disease-free survival

Discussion

It is well known that AML patients with a first CR duration of less than 1 year have a low chance of obtaining long survival or cure [8]. In particular, patients who relapse early after either autologous or allogeneic transplantation procedures have a poor clinical outcome [4, 6, 31]. Nonetheless, the achievement of CR2 may offer the opportunity of further treatment, including second transplantation procedures, provided that the toxicity of the salvage regimen is acceptable. Once CR2 is obtained, both ASCT and alloSCT may result in prolonged leukemia-free survival and cure [7, 21, 32]. Previous studies have shown that the combination of FAMP and ARA-C with G-CSF is highly effective and well tolerated by poor-risk AML patients as compared with other salvage schedules including high- or intermediate-dose ARA-C [9, 10, 23, 24, 35]. Comparable

CR rates have been obtained following FLAG plus either idarubicin or mitoxantrone, in both adults and children [5, 11, 25, 26]. In this study, we treated a cohort of 26 patients with poor-risk AML using the FLAG combination; in most cases the patients were in early relapse following ASCT. It should be noted that three patients (12%) had been autografted in CR2. In addition, most of these patients had received the current AML 10 EORTC/GIMEMA protocol, which includes an aggressive 3+5+10 induction schedule, followed by consolidation with ID-ARA-C and anthracyclines. Overall, 50% of the patients achieved CR, confirming that the FLAG is an effective regimen for relapsed AML, even in such a particularly unfavorable setting. The synergistic effect of FAMP plus ARA-C in enhancing ARA-CTP intracellular concentration [12] and the potential effect of FAMP plus ARA-C on multiple drug resistant cells [22] may account for the activity of FLAG in AML. It remains unclear whether the addition of idarubicin or mitoxantrone to FLAG results in a substantial improvement in terms of CR achievement and duration. It should be taken into account that all autografted patients have already received induction and consolidation regimens containing anthracyclines as well as conditioning regimens consisting of high-dose cytotoxic agents or TBI.

The toxicity of the regimen was acceptable, considering that most patients had been heavily pretreated. The treatment-related mortality was 15%, and only three patients (11%) died of infection (two fungal and one bacterial), while one died due to hemorrhagic complications. In a recent study dealing with resistant or relapsing pediatric AML patients treated with FLAG plus idarubicin, a similar incidence of induction death due to infections was observed [11]. In a further series including poor-risk adult AML patients, none of the 22 patients died of infectious complications [18]. However, in order to be included in the trial, patients had to be afebrile and free of infections; furthermore, there were no patients relapsing after transplantation procedures. In the study by Visani and co-workers (including five patients relapsing after ASCT), only one of 22 patients died of infection, confirming that the FLAG is associated with a low rate of life-threatening infections [35]. It is worthy of note that, as in Visani's study, we adopted a lower dose of G-CSF compared with the M.D. Anderson group, obtaining comparable results in terms of CR rate and tolerability. Which dose of G-CSF is best, and whether its prolonged administration has a role in protecting patients from infections remain unclear. In a nonrandomized study [10], Estey et al. compared two cohorts of AML/MDS patients treated with either FLAG or FAMP plus ARA-C. There were no differences as to CR or infection rates; however, most patients received treatment in rooms with laminar air flow until their granulocyte count reached 500 or 1000, and this may have accounted substantially for these results. In addition, all patients had newly diagnosed AML or myelodysplastic syndromes. In our study the situation was quite different, because patients in early relapse following ASCT were managed in single- or double-bed rooms; thus we cannot exclude that G-CSF may have played a substantial role in reducing fatal infections. As a matter of fact, while the potential benefit of growth factors in AML remains unclear where achievement and duration of CR are concerned, most published studies are in favor of a reduction of infections and hospitalization [3, 29].

Nonhematological toxicity was low, consisting mainly of mucositis and reversible liver dysfunction. There was only one episode of lethargy, which resolved spontaneously. The low toxicity of the regimen allowed the administration of an aggressive post-remission treatment to 11 of 13 patients (five second ASCT, two allo-BMT from matched, unrelated donors, and four HD-ARA-C). In conclusion, our results confirm that FLAG is an effective and well-tolerated regimen also for AML patients relapsing after ASCT. Given the relatively low toxicity, FLAG enables most patients to receive further treatment, including transplantation procedures aimed at long survival or cure.

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