FLAG-liposomal Doxorubicin (Myocet) Regimen for Refractory or Relapsed Acute Leukemia Pediatric Patients

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Summary: Despite the success in treating the majority of children with newly diagnosed acute leukemia, children with relapsed or refractory disease are an exceptionally difficult group of patients to cure. We assessed the combination of fludarabine with cytarabine and granulocyte colony-stimulating factor (FLAG) and nonpegylated liposomal doxorubicin (Myocet) in children with either acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML) refractory to first-line therapy or who had relapsed after risk-tailored chemotherapy. We treated 35 patients with FLAG-Myocet. The median age at treatment was 9 years and 7 months (range, 1 to 18 y). The 94% of ALL patients (16/17) and the 61% AML patients (11/18) achieved complete remission after FLAG-Myocet. A partial response was observed in the 17% of AML patients (3/18). Twenty-eight of 35 (80%) patients received hematopoetic stem cell transplantation in remission induced by FLAG-Myocet regimen. The ALL and AML overall survival at 3 years after FLAG-Myocet is 33% and 38%, respectively. The probability of ALL and AML event-free survival at 3 years after FLAG-Myocet is 33% and 40%, respectively. The probability of ALL and AML disease-free survival at 3 years after hematopoietic stem cell transplantation is 19% and 58%, respectively. Nonhematological toxicity was remarkably low, while almost all patients showed severe hematological toxicity. FLAG-Myocet is an efficient and a well-tolerated regimen that allows nearly all patients to undergo hematopoetic stem cell transplantation. FLAG-Myocet proved to be safe in terms of acute cardiac toxicity although particular care must be taken to reduce infectious complications due to severe myelosuppression. The promising results shown in our study need to be confirmed by larger and possibly randomized trials.

Key Words: acute leukemia, relapse, HSCT

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The prognosis of children and adolescents with acute leukemia has improved significantly over the past decades. Nowadays, significant improvements in primary therapy for childhood acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) have led to an overall cure rate of about 80% and 65%, respectively.[1–4] Despite these advances, approximately 20% of children with ALL and 30% to 50% with AML experience leukemia relapse, which remains the leading cause of treatment failure.[1,3,5] Currently, there is no uniform approach for treatment of relapse, but it is important to minimize the toxicity of reinduction therapy so that patients can proceed to hematopoetic stem cell transplantation (HSCT).

Antimetabolites are some of the most effective drugs against hematological malignancies. In particular, fludarabine is a fluorinated purine analog that proved to be active in the treatment of relapsed acute leukemias.[6–8] The combination of fludarabine with cytarabine and granulocyte colony-stimulating factor known as FLAG appears to have a synergistic effect and has been administered successfully in adults for the treatment of refractory/relapsed acute leukemias.[9–12] This regimen has also been used in several trials of combination therapies with other chemotherapeutic agents agents such as anthracyclines with an improvement of response rates but also an increased toxicity.[13]

The optimal use of anthracyclines in refractory/relapsed leukemias is restricted because of its dose-limiting cardiac, mucosal, and hematopoietic toxicity.[14] The liposomal entrapment of these chemotherapeutic drugs decreases their extensive uptake by the reticuloendothelial system and promotes a selective drug accumulation on leukemic cells reducing systemic toxicity.[15,16] Recent studies have utilized a combination of liposomal daunorubicin (DNX), fludarabine, and cytarabine in patients with poor risk acute leukemia and proved to be effective in inducing high complete response (CR) rates without the occurrence of significant toxicity.[16–18] Similarly, Melillo et al[19] reported the experience of the combination of nonpegylated liposomal doxorubicin (Myocet) with FLAG regimen in a cohort of adult poor prognosis AML patients. Myocet has a longer half life than standard doxorubicin, significantly less cardiotoxicity, and comparable antitumor efficacy.[20,21] This new combination showed promising efficacy even though a longer follow-up in a wider population was warranted.

Because of the unavailability of liposomal DNX in Europe, we assessed the FLAG-Myocet protocol in children with either ALL or AML refractory to first-line therapy or who had relapsed after risk-tailored chemotherapy.

MATERIALS AND METHODS

Selection of Patients

Between January 2006 and December 2009 35 children (23 boys and 12 girls) with refractory or relapsed ALL and AML attending the Pediatric Oncology/Hematology Units of Torino and Bologna, were treated with the FLAG-Myocet regimen. The median age at treatment was 9 years (y) and 7 months (mo) (range, 1 to 18 y).

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TABLE 1. Patients' Features and Outcome

Patient (Sex, Age*)	Disease	Treatment Before FLAG-Myocet (Cumulative Anthracycline Dose, mg/m^2)	Disease Status Before FLAG-Myocet	Response to FLAG-Myocet	Treatment After FLAG-Myocet (Months Between FLAG-Myocet and HSCT)	Relapse After FLAG-Myocet (mo)	Follow-up (mo)
1 (M, 9)	AML M5b	AIEOP LAM 2002-01 (0)	NR	CR	FLAG-HSCT (3)	No	Alive (42)
2 (M, 14)	AML M0 t(6;9)	AIEOP LAM 2002-01 (0)	NR	PR	FLAG-Myocet-HSCT (3)	No	Alive (52)
3 (F, 12)	AML M4 t(11;19)	AIEOP LAM 2002-01/HSCT (80)†	Relapse I	CR	FLAG-HSCT (2)	—	Dead‖
4 (M, 7)	AML M2 t(8;21)	AML-DCTER (125)†	Relapse I	CR	HSCT (3)	8	Dead‡
5 (M, 13)	AML M5	AIEOP LAM 2002-01(0)	NR	NR	None	—	Dead‡
6 (F, 17)	AML M5 t(1;3)	AIEOP LAM 2002-01/HSCT (80)†	Relapse I	CR	None	—	Dead§
7 (M, 12)	AML M2	AML-BFM 98 (310)†	Relapse I	CR	FLAG-HSCT (3)	No	Alive (27)
8 (M, 2)	AML M0	CCG 2961/HSCT (105)†	Relapse I (BM + CNS)	CR	FLAG	2	Dead‡
9 (M, 3)	AML M4 t(3;5)	AIEOP LAM 2002-01 (0)	NR	CR	FLAG-Myocet-HSCT (3)	No	Alive (24)
10 (F, 10)	AML M4	AML-BFM 95 + 2 VANDA (380) †	Relapse II	PR	FLAG-HSCT (3)	10	Dead‡
11 (M, 16)	AML	AIEOP LAM 2002-01/HSCT (80)†	Relapse I	NR	FLAG-Myocet	—	Dead‡
12 (M, 17)	AML	AML-BFM 2004 (310)†	Relapse I	PR	FLAG-HSCT (4)	—	Dead‖
13 (M, 18)	AML M4/M5 t(9;11)	ISG/OS-1 (490)	Secondary tumor	CR	FLAG-HSCT (3)	No	Alive (12)
14 (M, 15)	AML M5	AIEOP LAM 2002-01 (80)†	Relapse I	CR	HSCT (2)	No	Alive (6)
15 (M, 4)	AML M7	AIEOP LAM 2002-01 (0)	NR	CR	FLAG-Myocet-HSCT (5)	No	Alive (9)
16 (F, 12)	AML M1 del 7	AML-BFM 98/HSCT (NA)	Relapse I	NA	None	—	Dead§
17 (F, 10)	AML t(4;11)	AIEOP LAM 2002-01 (130)†	Relapse II (BM + CNS)	NR	None	1	Dead‡
18 (M, 9)	AML M2 t(8;21)	AML-BFM 2004 (180)†	Relapse II	CR	HSCT (2)	No	Alive (4)
19 (M, 4)	B precursors-ALL	AIEOP LLA 2000 (245)	Relapse I	CR	FLAG-HSCT (3)	6	Dead‡
20 (M, 6)	B precursors-ALL t(12;21)	AIEOP LLA 2000 (220)	Relapse I	CR	FLAG-HSCT (6)	36	Alive (36)
21 (M, 2)	B precursors-ALL t(4;11)	AIEOP LLA INTERFANT 99/HSCT (150)†	Relapse I	CR	FLAG-HSCT (2)	9	Dead‡
22 (F, 4)	B precursors-ALL	AIEOP LLA 2000 (220)	Relapse I	CR	FLAG-HSCT (3)	No	Alive (14)
23 (M, 16)	B precursors-ALL	AIEOP LLA 2000 (220)	Relapse I	CR	FLAG-HSCT (4)	6	Dead‡
24 (M, 1)	B precursors-ALL	INTERFANT 06 (150)†	Relapse I	CR	FLAG-HSCT (3)	No	Alive (21)
25 (F, 8)	B precursors-ALL	AIEOP LLA 2000 (220)	Relapse I	CR	FLAG-HSCT (3)	5	Dead‡
26 (M, 15)	B precursors-ALL	AIEOP LLA 2000 (150)	Relapse I	CR	FLAG-HSCT (4)	No	Alive (28)
27 (M, 10)	B precursors-ALL	ALL-BFM 2000-BFM REC96 (300)	Relapse II	CR	FLAG-HSCT (4)	7	Dead‡
28 (F, 15)	B precursors-ALL	AIEOP LLA 2000 (245)†	Relapse I	CR	FLAG-HSCT (2)	No	Dead§
29 (M, 5)	B precursors-ALL	8701 IVSS-CG (NA)	Relapse III	CR	FLAG-HSCT (6)	30	Dead‡
30 (F, 14)	B precursors-ALL	AIEOP LLA 9501 (120)	Relapse I	CR	HSCT (2)	2	Dead‡

TABLE 1. (*continued*)

Patient (Sex, Age*)	Disease	Treatment Before FLAG-Myocet (Cumulative Anthracycline Dose, mg/m^2)	Disease Status Before FLAG-Myocet	Response to FLAG-Myocet	Treatment After FLAG-Myocet (Months Between FLAG-Myocet and HSCT)	Relapse After FLAG-Myocet (mo)	Follow-up (mo)
31 (F, 14)	B precursors-ALL	ALL CAZED (240)†	Relapse III	NR	None	—	Dead‡
32 (F, 4)	B precursors-ALL t(12;21)	AIEOP LLA 2000 (320)	Relapse I	CR	FLAG-Myocet-HSCT (5)	9	Dead‡
33 (M, 8)	B precursors-ALL	AIEOP LLA 2000 (350)	Relapse I	CR	FLAG-HSCT (5)	No	Alive (18)
34 (F, 7)	B precursors-ALL	AIEOP LLA 2000 (220)	Relapse I	CR	FLAG-HSCT (11)	No	Alive (24)
35 (M, 15)	B precursors-ALL	AIEOP LLA 2000 (200)†	Relapse I	CR	FLAG-HSCT (3)	No	Alive (2)

*Age at FLAG-Myocet (y).
†Treatment before FLAG-Myocet includes high dose cytarabine.
‡Disease progression.
§Infectious complication.
‖HSCT-related complication.
ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete response; HSCT, hematopoetic stem cell transplantation; NA, not available; NR, no response; OS, overall survival; PR, partial response.

The criteria for receiving FLAG-Myocet were as follows:

1. Age at treatment between 0 and 18 years.
2. Patients never treated before with FLAG or FLAG-Myocet regimen.
3. Relapse in AML treated with standard AML therapy.
4. Early (> 18 mo from diagnosis and < 6 mo from stop therapy) or very early (< 18 mo from diagnosis) ALL first relapse in a child treated with standard ALL therapy and all ALL relapses after the first.
5. Persistence of blasts in AML after standard induction remission chemotherapy.
6. AML as a secondary malignancy.

Eighteen enrolled patients had a primary diagnosis of AML and 17 had ALL.

Twenty-nine patients (12 AML, 17 ALL) had relapsed disease. Five patients with AML had refractory disease, with persistent blasts present after initial remission induction chemotherapy. One patient experienced an early secondary malignancy (AML) diagnosed 3 years and 5 months after a primary osteosarcoma.

There were no strict rules with regard to previous treatment. Therefore, the patient group was heterogeneous as to the extent of pretreatment.

The characteristics of patients and the regimens which the patients had received before FLAG-Myocet are shown in Table 1.

All patients or their legal guardians signed written informed consent forms.

Treatment

The FLAG-Myocet protocol consists of PDN 60 mg/m^2/d intravenously (i.v.) from day −3 to day −1; granulocyte colony-stimulating factor 200 μg/m^2 i.v. from day −1 to day 5 and then from day 15 to remission (ie, stop on the first day of neutrophils $> 0.5 \times 10^9$/L); fludarabine 30 mg/m^2 i.v. by a 30-minute infusion (days 1 to 5), followed by 4 hours later by cytarabine 2 g/m^2 by a 3-hour infusion (days 1 to 5); Myocet 50 mg/m^2 by a 2-hour infusion (days 1, 3, and 5). Methotrexate intrathecally (< 1 y, 6 mg; ≥ 1 y < 2 y, 8 mg; ≥ 2y < 3 y, 10 mg; ≥ 3 y, 12 mg) was administered on day 1. Dose calculation was based on body surface area obtained from height and actual weight.

Responding patients underwent allogenic HSCT if a suitable donor was immediately available, or time-to-transplant could be bridged by a second course of consolidation chemotherapy based on FLAG with or without Myocet.

Toxicity

The toxicity of the FLAG-Myocet regime was assessed using the Common Toxicity Criteria (World Health Organization).

Clinical Response

Bone marrow aspirates were performed after FLAG-Myocet upon hematological recovery (neutrophils $> 0.5 \times 10^9$/L; platelets $> 100 \times 10^9$/L) to assess response.

Response to treatment was assessed using morphological analysis. CR was defined as an absence of physical signs of leukemia or detectable leukemia cells on peripheral blood smears, ≤ 5% leukemic blasts in bone marrow with evidence of normal hematopoiesis. Partial remission (PR) was defined as normocellular marrow containing between 5% and 25% of leukemic blast cells. The achievement of CR or PR was considered as response. On the contrary,

patients who achieve neither CR nor PR were defined as nonresponders (NRs). Relapse disease was defined as > 5% blasts in a bone marrow that had previously achieved CR.

Supportive Therapy

All patients were hospitalized for treatment. Supportive therapy was administered according to protocols active in each institution. All children were given prophylactic antibiotics (ciprofloxacin or amoxicillin conjugated with clavulanic acid) and broad-spectrum antibiotics were given in accordance with the febrile neutropenia protocol of each Department. Fluconazole was administered to prevent fungal infections in all patients and it was modified if there was clinical evidence of proven/probable fungal infections.

Cotrimoxazole or pendamidine aerosol was administered to all patients as prophylaxis against *Pneumocystis carinii* infection. Prophylactic steroid eye drops were administered to all patients while receiving cytarabine.

Statistical Analysis

Survival analysis was carried out using the Kaplan-Meier method. Event-free survival (EFS) was calculated from the start of FLAG-Myocet up the last follow-up or relapse-related or treatment-related mortality, whichever occurred first. Disease-free survival (DFS) was calculated from HSCT until relapse or death resulting from any cause.

RESULTS

ALL Patients

Seventeen ALL patients were included in this study. Fourteen ALL patients were in the first relapse, 1 the in second, and 2 in the third relapse at the time they received FLAG-Myocet. The median duration of the first remission was 25 months (range, 3 to 53 mo). All but 1 ALL patient received FLAG-Myocet chemotherapy before HSCT.

Sixteen of 17 (94%) ALL patients achieved CR after a first course of FLAG-Myocet. CR was achieved in all patients in first relapse (14/14), in 1 patient in the second, and in 1 in the third relapse. One patient in the third relapse was a NR.

All 16 responder patients were subsequently transplanted, 14 after a following FLAG course, 1 after a second FLAG-Myocet and the last 1 was transplanted directly after the first FLAG-Myocet. The median duration of remission after FLAG-Myocet was 9 months (range, 2 to 36 mo).

Among 16 responder patients, 6 patients are alive and are in continuous remission (median, 27 mo; range, 2 to 36 mo) and 9 relapsed after FLAG-Myocet at a median of

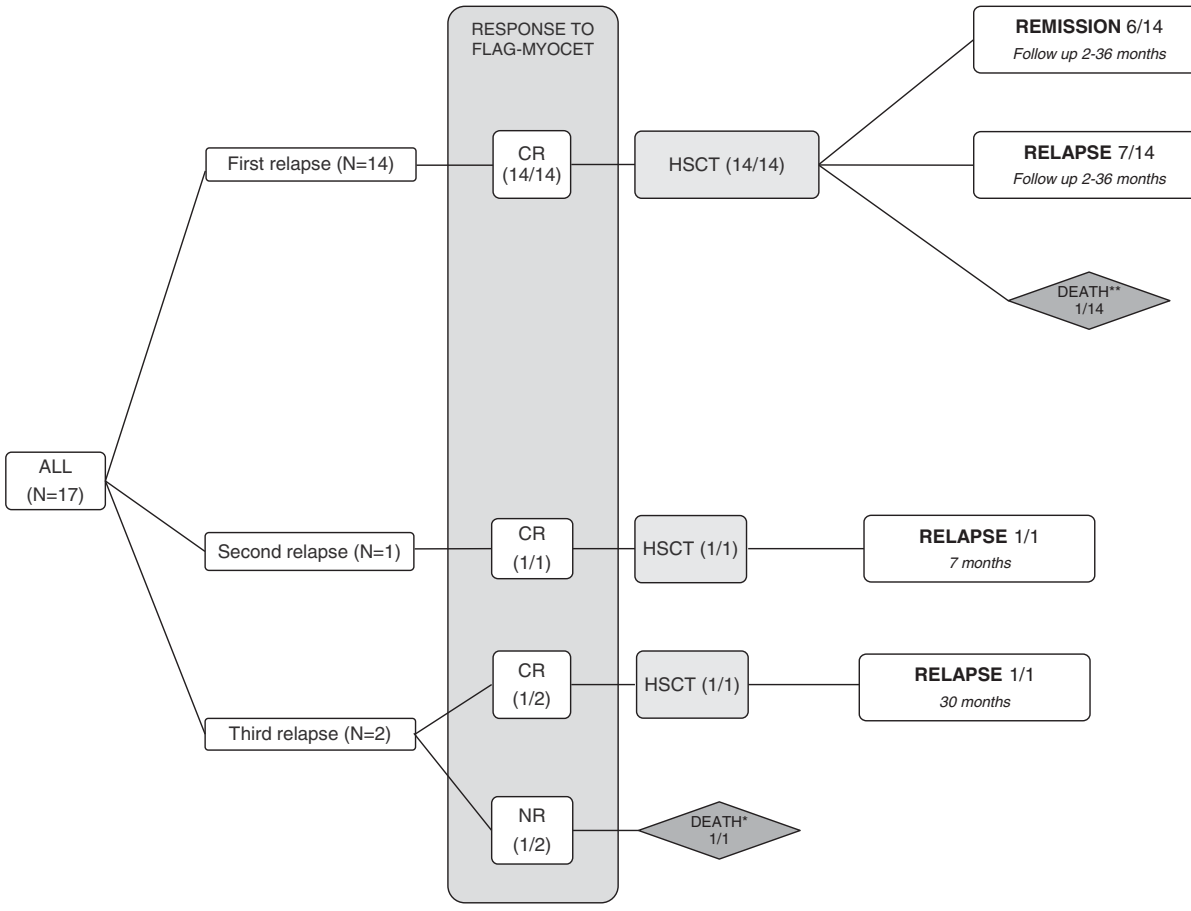

FIGURE 1. ALL response to FLAG-Myocet. ALL indicates acute lymphoblastic leukemia; CR, complete response; HSCT, hematopoetic stem cell transplantation; NR, no response; *Disease progression; **Infectious complication.

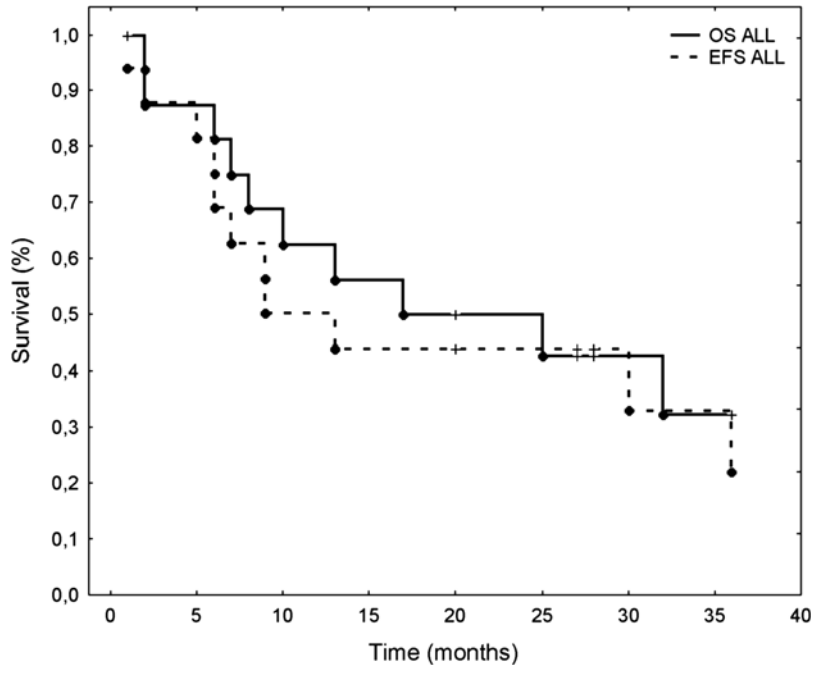

FIGURE 2. ALL EFS and overall survival after FLAG-Myocet. ALL indicates acute lymphoblastic leukemia; EFS, event-free survival.

8 months (range, 2 to 36 mo). One patient who was disease free died of bacterial infection. One of 17 ALL patient was NR and died after 4 months of FLAG-Myocet (Fig. 1).

The probability of EFS and overall survival at 3 years is 33% (Fig. 2). The probability of DFS at 3 years after HSCT is 19% (Fig. 3).

AML Patients

Eighteen AML patients were included in this study and treated with FLAG-Myocet.

Twelve patients had relapsed disease (9/12 first relapse, 3/12 second relapse), 5 had refractory disease and the last 1 developed secondary AML 3 years and 5 months after a

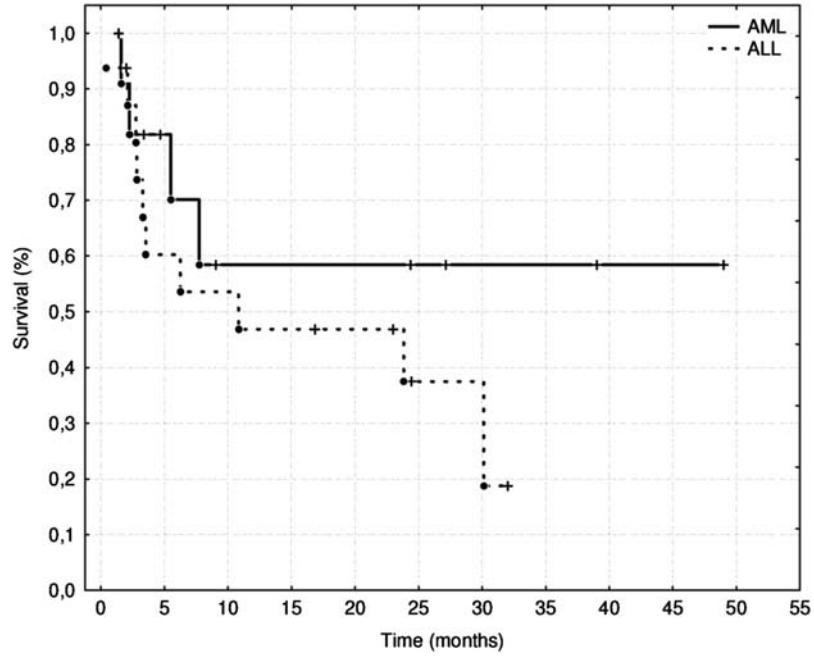

FIGURE 3. ALL and AML DFS after HSCT. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; DFS, disease-free survival; HSCT, hematopoetic stem cell transplantation.

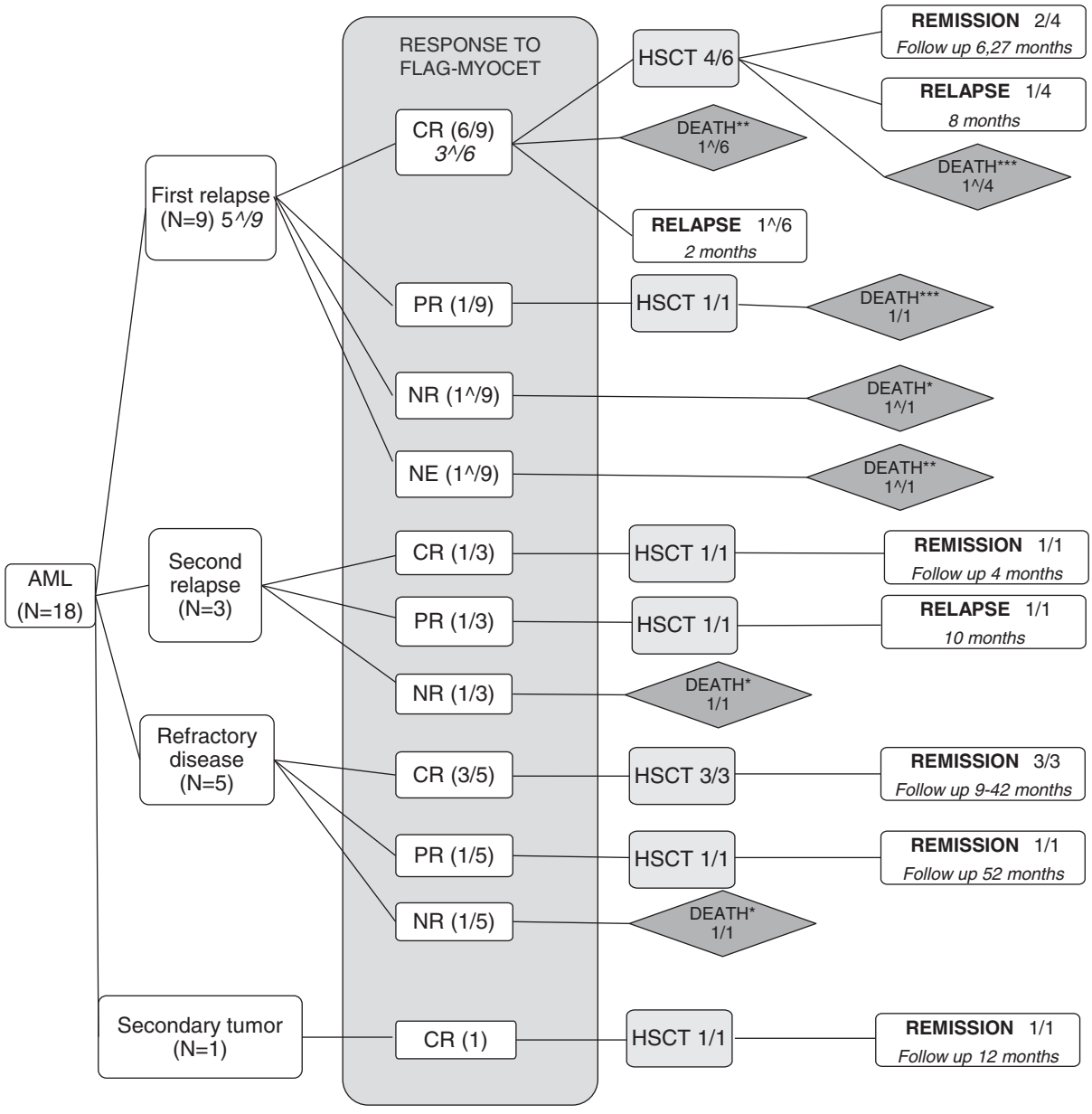

FIGURE 4. AML response to FLAG-Myocet. AML indicates acute myeloid leukemia; CR, complete response; HSCT, hematopoetic stem cell transplantation; NR, no response; PR, partial response; *Disease progression; **Infectious complication; ***HSCT-related complication; ^FLAG-Myocet performed after a previous HSCT.

primary diagnosis of osteosarcoma. The median duration of the first remission was 12 months (range, 4 to 19 mo).

Five of 12 relapsed patients received FLAG-Myocet after HSCT; all 5 AML patients with refractory disease received FLAG-Myocet as their second-line chemotherapy within 1 month of their initial diagnosis, and none of them had been previously transplanted.

Fourteen of 18 (14/18, 78%) patients achieved remission after FLAG-Myocet: CR was observed in 61% (11/18) and PR in 17% (3/18) of responder patients.

Three patients were NR (1 refractory AML, 1 in the first and 1 in the second relapse) and died within 2 months after FLAG-Myocet for disease progression. One patient died at day +20 after FLAG Myocet due to infection complication before bone marrow assessment.

The median remission duration after FLAG-Myocet was 9 months (range, 1 to 52 mo).

Twelve of 14 responder patients were subsequently transplanted: 2 patients relapsed after HSCT with a median of 9 months (range, 8 to 10 mo), 2 patients died of HSCT-related complications, and 8 patients are alive and in continuous remission 18 months after FLAG-Myocet (range, 4 to 52 mo).

Two responder patients were never transplanted, 1 patient experienced a relapse only after 2 months from

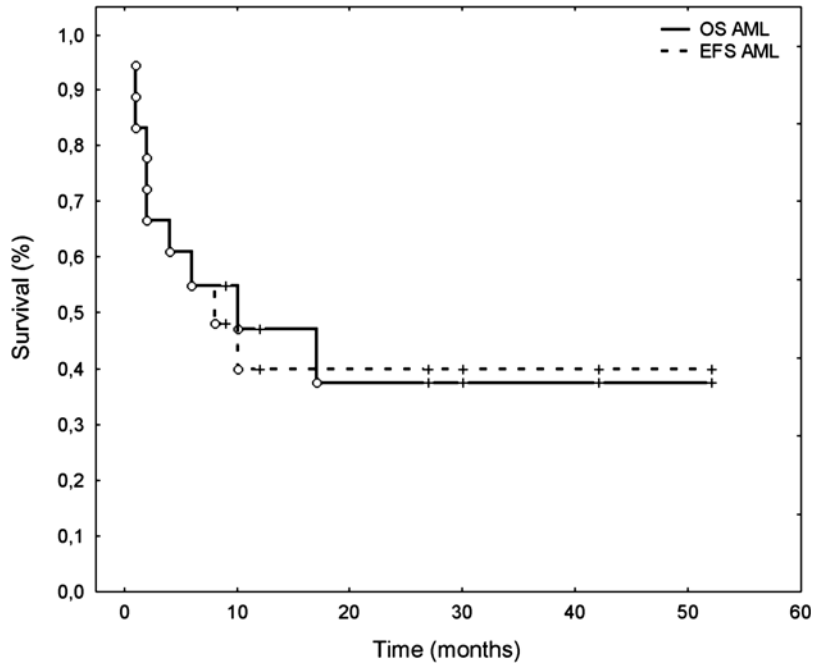

FIGURE 5. AML EFS and overall survival after FLAG-Myocet. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; EFS, event-free survival.

FLAG-Myocet before HSCT, and the other patient died of fungal infections free of disease 1 month after FLAG-Myocet.

All 5 patients who received FLAG-Myocet after a previous HSCT died precociously within 4 months from FLAG-Myocet (Fig. 4). The probability of EFS and overall survival at 3 years is 40% and 38%, respectively (Fig. 5). The DFS probability at 3 years is 58% (Fig. 3).

Hematological Toxicity

All patients had severe myelosuppression and required intensive support. The median duration of the time before the neutrophils recovered to a level time $> 0.5 \times 10^9$/L was 18 days with a range of 10 to 61 days. The median duration of time for platelets to recover to a level $> 50 \times 10^9$/L was 22 days with a range of 14 to 88 days. The median number of days with febrile neutropenia was 15 (range, 5 to 36 d). Three patients died from infectious complications, 2 patients from invasive fungal infections after 1 month from FLAG-Myocet, and the other from pneumonia of unknown origin after a second FLAG course and a subsequent allogenic HSCT.

Nonhematological Toxicity

The nonhematological toxicity was mild. Most patients developed grade 3 or 4 gastrointestinal toxicity, with mucocytis being most commonly reported. There was no other grade 4 toxicity. There was no serious acute CNS or cardiac toxicity.

DISCUSSION

Despite the success in treating the majority of children with newly diagnosed acute leukemia, children with relapsed or refractory disease are an exceptionally difficult group of patients to cure.

The use of FLAG alone or in association with other chemotherapeutic agents resulted in an effective regimen even though limited data about its use in pediatric treatment of relapsed/refractory acute leukemias are present in literature.[13,16,22–25]

McCarthy and colleagues showed the results of FLAG regimen in a heterogeneous group of 19 children heavily pretreated with intensive multiagent chemotherapy because of multiple relapses or primary resistant acute leukemias. Twelve patients had a primary diagnosis of AML, 4 patients had ALL and 3 patients had biphenotypic leukemia. Six patients with AML and 2 with biphenotypic leukemia had refractory disease, with persistent blasts present after initial remission induction chemotherapy. Eleven patients (6 AML, 4 ALL, and 1 biphenotypic) had relapsed disease. Five patients were in the first relapse, 4 in the second, and 2 in the third at the time they received FLAG. An overall CR rate of 70% with a PR rate of 20% was reached. The toxicity of the regimen proved to be acceptable. Although all patients suffered prolonged neutropenia, only 1 episode of severe sepsis was experienced.[22] The addition of anthracyclines seems to improve the antileukemic activity of FLAG even though the cumulative toxicity and mainly drug-induced cardiotoxicity limit their administration especially in heavily pretreated patients.

Fleischhack et al[13] documented a CR rate of 81% in 21 poor-prognosis AML pediatric patients treated with the combination of FLAG regimen with Idarubicine (FLAG-IDA); the main early toxicity was long-term myelosuppression associated with a high incidence of infections.

The availability of formulation consisting of anthracyclines entrapped within liposomes allows anthracycline-antileukemic activity to be exploited without adding significant toxicity. In fact, liposomal anthracyclines are characterized by higher tumor cell delivery, improved

pharmacokinetic and therapeutic indices, and therefore by a reduced toxicity profile.[26]

Recently, the International BFM study group showed the preliminary results from the International Randomised Phase III study relapsed AML 2001/01 based on randomization of FLAG against FLAG/DNX in the first reinduction course.[18] The combination of liposomal DNX improves treatment response; patients randomized to FLAG/DNX had a 12% higher early good response rate than patients randomized to FLAG alone (81% vs. 69%, $P < 0.05$). The early response was defined based on bone marrow examination shortly before a second reinduction course (FLAG only), and defined as either good ($\leq 20\%$ leukemic blasts) or poor ($> 20\%$ leukemic blasts). Overall survival was also higher with DNX, albeit not significantly, whereas short-term toxicity of FLAG-DNX was similar to FLAG alone.[18]

Here, we report the experience of a combination of FLAG with Myocet in 35 pediatric patients with refractory/relapsed acute leukemia. All of them had been pretreated with heterogeneous multiagent chemotherapy. We decided to assess the use of Myocet in combination with FLAG instead of liposomal DNX because of its recent unavailability in Europe.

A response after 1 course of FLAG-Myocet of 94% for ALL and 78% for AML is extremely encouraging. The FLAG-Myocet regimen showed remarkable activity in inducing remission in ALL patients who relapsed after risk-tailored treatment. In particular, all ALL patients in first relapse achieved a complete remission after a single FLAG-Myocet course. Only 1 patient in third relapse achieved neither complete nor partial remission. This patient had already been heavily treated with high-dose therapy.

Among the AML patients, the FLAG-Myocet regimen showed elevated antileukemic activity not only in relapsed patients, but also in those who were refractory to induction treatment. In fact, 80% (4/5 patients) of AML patients refractory to induction showed a good response (3/4 complete response, 1/4 partial response) after the first FLAG-Myocet course. On the other hand all patients (5/5) who had performed a previous HSCT died within few months from FLAG-Myocet.

Our experience of relapsed AML is in line with the preliminary results from the International Randomized Phase III study relapsed AML 2001/01 reported by the International BFM study group. We observed a response in 82% of relapsed AML patients, which is comparable with the 81% reported in patients randomized to FLAG-DNX.

Taking into account these results, HSCT procedures were performed in a high proportion of patients (28/35, 80%) enrolled in our study, allowing them to attempt leukemia eradication. A particular encouraging 3 years DFS probability of 58% was observed in AML patients (12/18) who received HSCT.

On the whole, the association of FLAG-Myocet caused acceptable hematological and extrahematological toxicity, with early deaths occurring in just 2 cases. The most common side effects were hematological and gastrointestinal toxicity, especially with mucositis. Furthermore, no patient showed severe acute heart toxicity. However, careful cardiac monitoring is recommended in this population to identify potential late side effects.

In conclusion, FLAG-Myocet was used in a very–high-risk group of children with relapsed or refractory acute leukemias resulting in an effective regimen with an encouraging remission rate for treatment of these patients.

The toxicity is acceptable and has allowed nearly all patients to undergo further HSCT. In particular, Myocet proved to be safe in terms of acute cardiac toxicity although particular care must be taken to reduce infectious complications due to severe myelosuppression.

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