Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of relapsed or poor risk childhood acute leukemia

Nevin Yalman[1], Nazan Sarper[1], Ömer Devecioğlu[1], Sema Anak[1], Ertuğrul Eryılmaz[1] Mehmet Can[2], Harun Yenilmez[2], Leyla Ağaoğlu[1], Gündüz Gedikoğlu[3]

[1]Department of Pediatrics, İstanbul University [2]Faculty of Medicine and [3]Division of Pediatric Hematology-Oncology, Our Children Leukemia Foundation Medical Centre, İstanbul, Turkey

SUMMARY: Yalman N, Sarper N, Devecioğlu Ö, Anak S, Eryılmaz E, Can M, Yenilmez H, Ağaoğlu L, Gedikoğlu G. Fludarabine, cytarabine. G-CSF and idarubicin (FLAG-IDA) for the treatment of relapsed or poor risk childhood acute leukemia. Turk J Pediatr 2000; 42: 198-204.

The prognosis of relapsed acute leukemia or chronic leukemia in acute blast crisis is poor and new chemotherapeutic regimens could be useful for these patients. Six relapsed acute lymphoblastic leukemia (ALL), nine relapsed acute myeloblastic leukemia (AML), one chronic myelomonocytic leukemia (CMML) and one chronic myeloid leukemia (CML) in acute blast crisis between three to 18 years (median 10 years) received fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) chemotherapy (CT). Five of the AML relapses were after bone marrow transplantation (BMT) and four were recurrent relapses. At the end of the second course only three patients (2 AML, 1 ALL) were in complete remission (CR). Of the three patients in CR, one patient with AML had her first donor lymphocyte transfusion (DLT) on the 7th day of the second FLAG-IDA course and she is disease-free on the 30th month of the second remission. The remaining two patients were transplanted from unrelated donors in a BMT center abroad on the 5th and 8th month of the last remission and both died with BMT-related complications. Out of 25 courses, seven resulted in fatal infections. The regimen was ineffective in B-cell ALL as in acute blastic crisis of CMML and CML. We could not evaluate the remission-inducing effect accurately in most of the patients due to induction failure. FLAG-IDA appears to be a myelotoxic therapy for relapsed or poor risk leukemia in a developing country. It is not cost-effective; dose modifications or a regimen without IDA may be tried if there is an available marrow donor.

Key words: fludarabine, childhood, leukemia, FLAG, idarubicin.

Despite high remission rates in de novo childhood acute leukemia, relapse is still a serious problem and complete remission (CR) rates of relapse regimens are not satisfactory. In a recent report of the Children's Cancer Study Group, rates of six year survival in acute lymphoblastic leukemia (ALL) after isolated bone marrow (BM), central nervous system and testis relapse were 20, 48 and 70 percent, respectively. Rates of survival after isolated BM relapse at 0-17 months, 18-35 months and after 36 months were six, 11 and 43 percent, respectively[1].

Bone marrow transplantation (BMT) is an effective first line treatment in poor prognosis ALL, acute myeloblastic leukemia (AML) or in chronic myeloid leukemia (CML), but relapse after BMT is generally considered incurable and has not been standardized[2].

In the light of report that FLAG-IDA (fludarabine, cytarabine, G-CSF, and idarubicin) is effective in the treatment of children and adolescents with relapsed AML and chronic myelomonocytic leukemia (CMML) in acute blast crisis[3] and that a complete remission rate of 58-63 percent can be achieved in adult AML and myelodysplastic syndrome (MDS)/AML[4,5], we started FLAG-IDA chemotherapy (CT) for children and adolescents with poor prognosis leukemia (relapsed AML, ALL and CMML, CML in blast crisis). Visani et al.[6] and Montillo et al.[7] also used FLAG in relapsed or primary resistant ALL with a CR rate of 67 percent (8/12) and 83 percent (10/12), respectively.

Fludarabine (9-B-D-arbine-fluranosyl-2 fluoroadenine) is a synthetic purine analogue. Its anti-tumor activity is by termination of DNA and RNA synthesis, inhibiting DNA and RNA polymerases, DNA primase, DNA ligase and ribonucleated reductase, and by potentiation of deoxyctidine kinase activity. It also induces apoptosis[8] and potentiates the activity of anti-tumor agents by modulating metabolism of cytarabine[9]. Fludarabine increases the accumulation of Ara-CTP (active triphosphate metabolite) in leukemic blasts by a median 1.7 fold in vitro studies[9]. Co-administration of G-CSF to patients receiving fludarabine plus cytarabine (FLAG) was based on reports that G-CSF shortened the duration of neutropenia and reduced infection rates following completion of CT[10]. Additionally, in vitro studies suggest that G-CSF administered shortly before, during and a short time after Ara-C can make myelogenous leukemia cells more sensitive to the drug by recruiting quiescent cells into the cell cycle and increasing Ara-C phosphorylation[11,12]. An anthracycline is also combined to the FLAG regimen to increase response to CT. Besides its antileukemic activity, idarubicin is less cardiotoxic[13], which is an important factor for heavily pre-treated relapsed patients.

Material and Methods

Between March 1997-July 1998, six relapsed ALL, nine relapsed AML, one CMML and one CML in acute blast crisis between three to 18 years (median 10 years) were treated with FLAG-IDA regimen after informed consents of parents and/or patients were obtained. Two patients had B-cell ALL (L_3), three B precursor ALL, one T-cell ALL, one AML-M_0, two M_2 two M_4 and four M_5. Five patients with AML had post-BMT relapses (3 after allogeneic-BMT from matched siblings, 1 after auto-BMT, and 1 after autologous peripheric blood stem cell transplantation) at a median of six months (3-7 months). Three patients were in the second, one patient in the third and the rest in the first relapse. All patients had marrow relapse which was associated with extramedullary disease in five (2 testis, 2 central nervous system, 1 bone). Duration of first remission of patients with acute leukemia was ≤six months in three patients, seven to 17 months in seven patients, 18-35 months in four patients and ≥36 months in one patient. Patients with chronic leukemia were on the 24th and 48th months of hydroxyurea and interferon-alpha therapy at the time of acute blastic transformation. AML-MRC-10, BFM-86 ALL and BFM-90 B-cell ALL protocols were administered to patients as first line therapy. Busulfan-cyclophosphamide regimen without irradiation was used as conditioning for BMT.

Cardiac (left ventricle ejection fraction >60), renal (urea, creatinine, creatinine clearance) and hepatic functions (transaminases, bilirubin) were evaluated before CT. Patients were eligible if these functions were within normal limits. The patients received therapy in isolated rooms and all had central venous catheters (Hickmann). In addition to intravenous immunoglobulin (0.2 g/m^2/kg twice a week), amphotericin B and ceftazidime inhalation (2x4 mg/day and 2x1g/day, respectively) were also administered as prophylaxis in the last seven patients. An antiemetic drug (ondansetron) was also used throughout the chemotherapy courses. Total parenteral nutrition, intravenous antibiotics and antifungal agents were administered according to current protocols when necessary. Irradiated blood products were used. A bone marrow aspirate was performed upon hematologic recovery (neutrophils >1x10^9/L, platelets >100x10^9/L). CR was defined as evidence of normal hematopoietic regeneration (neutrophils >1x10^9/L, platelets >100x10^9/L), with <5% blasts), and partial remission was defined as reduction in marrow blasts to at least 50 percent. A second course of FLAG-IDA was planned after the first course. Patients in CR and with a suitable bone marrow donor underwent allogeneic BMT; donor lymphocytes were transfused to patients relapsing after allogeneic BMT.

Treatment Regimen: G-CSF beginning on day 0 was continued up to absolute neutrophil count (ANC)>1000 µl, with 400 µg/m^2/d administered intravenously over 30 minutes; fludarabine (30 mg/m^2) was administered intravenously over 30 minutes, daily for five consecutive days; high dose cytarabine (2000 mg/m^2) was administered for five consecutive days intravenously over four hours, starting four hours after fludarabine; idarubicin (10 mg/m^2) was administered on days two to four intravenously over 30 minutes. The idarubicin dose was reduced to 8 mg/m^2 in the last five patients to reduce myelosuppression.

Results

A total of 25 courses were administered to 17 patients. Patients' characteristics and outcomes are shown in Table I.

Table I. Patients' Characteristics and Response to FLAG-IDA Chemotherapy

Patient	Sex/age at FLAG-IDA, (year)	Diagnosis	Duration of first remission	Response to FLAG-IDA	Overall survival	Survival following 1 FLAG-IDA Outcome
1	M, 8	ALL-second marrow, testis relapse	36 mo.	CT 1: Persisting marrow aplasia	44 mo.	33 d-died with infection
2	M, 10	ALL-T-cell, first marrow, testis, CNS relapse	6 mo.	CT 1: Persisting marrow aplasia	8 mo.	47 d-died with infection
3	F, 3	ALL-L_3, first marrow relapse	16 mo.	CT 1: No reponse	19 mo.	80 d-died with resistant disease
4	M, 4	ALL-L_3, first marrow and bone relapse	6 mo.	CT 1: No response	7 mo.	30 d-died with resistant disease
5	F, 10	ALL-first marrow relapse	20 mo.	CT 1: Persisting marrow aplasia	21 mo.	26 d-died with infection
6	M, 15	ALL-third marrow relapse	48 mo.	CT 1: CR, CT 2: CR	12 years +	11 mo-died with BMT** related complications
7	F, 14	AML-M_2-marrow relapse after AlloBMT	13 mo.	CT 1: Persisting marrow aplasia	14 mo.	35 d-died with infection
8	F, 17	AML-M_4, first marrow relapse after auto PBSCT	14 mo.	CT 1: Persisting marrow aplasia	15 mo.	37 d-died with infection
9	M, 13	AML-M_2, second marrow relapse	6 mo.	CT 1: CR, CT 2: no response	36 mo.	6 d-died with resistant disease
10	M, 14	AML-M_5, second marrow relapse	20 mo.	CT 1: CR, CT 2: CR	39 mo.	7.5 mo-died with BMT*** related complications
11	M, 13	AML-M_5, first marrow relapse after AlloBMT	19 mo.	CT 1: Persisting marrow aplasia	20 mo.	35 d-died with infection
12	F, 3	AML-M_5, first marrow relapse after AlloBMT	13 mo.	CT 1: CR, CT 2: CR	39 mo.	30 mot-disease free after three donor lymphocyte transfusions
13	M, 15	AML-M_5, first marrow relapse	9 mo.	CT 1: CR, CT 2: Persisting marrow aplasia	11 mo.	63 d-died with infection
14	M, 8	AML-Mo, first marrow relapse after AlloBMT	11 mo.	CT 1: no response	13 mo.	60 d-died with resistant disease
15	M, 10	AML-M_4, first marrow and CNS relapse	7 mo.	CT 1: no response, CT 2: no response	10 mo.	85 d-died with resistant disease
16	F, 45	CMML-acute blast crisis	*24 mo.	CT 1: no response, CT 2: response	34 mo.	10 mo-died with resistant disease
17	F, 18	CML-acute blast crisis	*48 mo.	No response	54 mo.	6 mo-died with resistant leukemia

* duration of chronic phase.
** mis-matched unrelated donor.
*** MUD: matched-unrelated donor.

CNS : central nervous system.
PBSCT : peripheric blood stem cell transplantation.
d : days.
mo : months.
CT : chemotherapy.
CR : complete remission.
ALL : acute lymphoblastic leukemia.
AML : acute myeloblastic leukemia.
AlloBMT : allogeneic bone marrow transplantation.
CMML : chronic myelomonocytic leukemia.
CML : chronic myeloid leukemia.

Toxicity: Nausea and vomiting were not serious problems and were controlled with antiemetics. There was no acute neurological, cardiac or renal toxicity. Two patients developed hyperbilirubinemia and hepatic failure associated with severe infections. Recovery of blood counts and incidence of infection: duration of neutropenia (ANC<500x10^9/L) was a median of 32 days (18-42 days) and of thrombocytopenia (<30.000x10^9/L) 27 days (7-38 days) in eight courses resulting in CR. Patients experienced infection episodes in every course. Nine patients (9/17:52.9%) had severe mucositis and one had oral herpetic lesions. Infection episodes were febrile neutropenia (6/25), septicemia (8/25), pneumonia (10/25), enteritis (2/25), sinusitis (2/25) and cellulitis (1/25). Hemoculture isolates were Staphylococcus aureus (4 episodes), Enterobacter (1 episode), Escherichia coli and Candida spp. (1 episode). Pseudomonas aeruginosa (oral lesion), Staphylococcus aureus (throat culture, urine culture), and Candida spp. (throat culture) were other isolates. Two patients had Aspergillus antigenemia and one patient had radiological findings suggesting pulmonary aspergillosis. Seven courses (7/25: 29%) resulted in fatal infections without marrow recovery in a median of 35 days (26-47 days).

Treatment Outcome: Response to FLAG-IDA CT courses and post-CT BMT and DLT (donor lymphocyte transfusion) procedures are shown in Table II. At the end of two CT courses there were only three patients in CR (2 AML and 1 ALL). One patient with AML had DLT on the 7th day of the second FLAG-IDA course. After recovery she had one cycle of Capizzi II (cytosine arabinoside 3g/m^2x4 and L-asparaginase 6000 U/m^2x1) and a second DLT on the 7th day. Then maintanence therapy cycles (cytosine arabinoside 60 mg/m^2 for 4 days and 6-thioguanine for 28 days) were administered for 12 months; at the end of maintenance therapy, a 3rd DLT was given without any complication. She is disease free with a 100 percent Karnofsky score at the 15th month of the 3rd DLT. The remaining two patients who had BMT from unrelated donors in a BMT center abroad at the 5th and 8th months of the last remission died with BMT-related complications (Table II). The patient who had veno-occlusive disease (VOD) during BMT was treated with interferon-alpha for chronic hepatitis C infection and was cured before the leukemia relapse.

Cost of Therapy: Cost of therapy including chemotherapy, G-CSF and supportive measures (antibiotics, antifungal agents, intravenous immunoglobulin, parenteral nutrition and blood products) was a median of 20,400 U.S. dollars ($ 16,000-$ 116,000 dollars) per course.

Discussion

Experience with fludarabine in leukemia cases in children and adolescents is quite limited. In 1996, Fleischhack et al.[3] reported initial results of a pilot study with FLAG-IDA in the treatment of recurrent AML in children and adolescents. In 1997, Dinndorf et al.[14] and Leahey et al.[15] used idarubicin with fludarabine and cytarabine for refractory or recurrent pediatric acute leukemia. In 1998, Fleischhack et al.[16] reported that 17/23 patients with a median age of 7.7 years achieved CR with a median duration of 13.5 months. Eleven patients underwent BMT or peripheric blood stem cell (PBSC)

Table II. Summary of Response to FLAG-IDA Courses and Post-Chemotherapy BMT and Donor Lymphocyte Transfusion Procedures

Diagnosis	All patients n	Response to 1st FLAG-IDA	Response to 2nd FLAG-IDA CT	Post-CT BMT/DLT CT	Outcome
ALL	6	1 CR	1 CR	1 BMT*	BMT-related early death with CMV pneumonia
AML	9	4 CR	2 CR	1 BMT (MUD)	BMT-related early death with VOD
				1 DLT	Disease-free at 30 month of first FLAG-IDA
CMML	1	No response	No response	–	Died with resistant disease
CML	1	No response	–	–	Died with resistant disease

* one mis-matched unrelated donor.

DLT : donor lymphocyte transfusion.
CR : complete remission.
VOD : veno-occlusive disease.
MUD : matched unrelated donor.
AML : acute myeloblastic leukemia.
CML : chronic myeloid leukemia.
CMV : cytomegalovirus.
CT : chemotherapy.
BMT : bone marrow transplantation.
ALL : acute lymphoblastic leukemia.
CMML : chronic myelomonocytic leukemia.

transplantation following FLAG-IDA-FLAG regimen, and overall nine patients remained in CR with a median duration of 17.5 months (9.5-39 months). But eight of 23 patients received only a single FLAG-IDA course and two received FLAG alone. The initial recommendation of FLAG-IDA was changed to FLAG courses for myelotoxicity. Based on their data their conclusion was that a FLAG-IDA regimen with FLAG-IDA as a reinduction course and FLAG as consolidation therapy is an effective therapy prior to allogeneic and autologous BMT or PBSCT. In our study group, induction failure was higher and the outcome was disappointing. Five of nine AML patients had relapsed post-BMT and two patients had second marrow relapse. In their series, none of the patients were post-BMT relapse cases and only two patients were on second relapse. Additionally, neutropenia was shorter in that study (median 22.5 days, range 14 to 42 days). Our patients' longer marrow aplasia and higher CT-related deaths might be attributed to their heavily pre-treated state. In Fleischhack et al.'s[16] series, only three patients were treated with two courses of FLAG-IDA[16]. FLAG-IDA courses were more myelosuppressive than FLAG courses. In our series, CR was induced in patient 13 with one course of FLAG-IDA; however, he could not tolerate the second course. Fleischhack et al.[16] also reported pulmonary infections as the main non-hematological toxicity, and there were three therapy-related deaths.

The FLAG-IDA regimen seems ineffective in acute B-cell leukemia. Two patients with B-cell leukemia died with resistant disease. Two patients with B-precursor ALL and one with T-cell ALL died with infection before marrow recovery. Patient 6 completed two courses with CR without severe infections, but his previous relapses were all responsive to CT, with long remission duration. The regimen was also unsuccessful in inducing remission in acute blastic transformation of CML and CMML.

Time of relapse is an important prognostic variable in leukemia. In the MRC UKALL X study, only three of 106 children with marrow or combined relapse within two years or less of completing therapy were in second CR[17]. Four out of six ALL patients in our series relapsed within two years of remission.

In a more recent report on FLAG for therapy in refractory or high-risk relapsed ALL and AML in children, 13/16 (70%) patients achieved CR, and 4/16 partial remission (PR)[18]. Thirteen patients received BMT as consolidation, and seven patients were alive at 12 months post therapy. In that study, McCarthy et al.[18] preferred to avoid anthracyclines for inducing remission in heavily pre-treated children, and concluded that FLAG is an effective regimen. We did not observe acute cardiac toxicity, but Fleischhack et al.[16] reported cardiac toxicity in three of 24 FLAG-IDA courses. Acute cardiac toxicity is generally acceptable, but all authors emphasize pulmonary infections during CT or post-transplant[16,18]. The high rate of pulmonary infections could have been caused by toxic injury of the lung epithelial cells, by cytostatic drugs, or by the long-term neutropenia involving a risk for fungal infections[19]. Purine analogues such as fludarabine produce long term T-helper cell depletion involving a high risk for opportunistic infection[20]. Although we used liposomal amphotericin and ceftazidime inhalation for prophylaxis during CT of our last seven patients, only three of them completed CT without pulmonary infection. Neutropenia was quite long, despite G-CSF. Laminar air flow rooms may also reduce infections.

Other CT alternatives for primary resistant or relapsed AML also result in low CR rates but with lower induction death rates[21].

Second BMT or DLT must be pursued as soon as CR is achieved, because CRs after post-BMT relapses are generally short lived[22]. Second transplants with a different cytoreductive regimen can eradicate disease resistant to prior myeloablative treatment[22]. Outcomes of second transplants were better in AML compared to ALL[23]. Unfortunately, only one of our patients with post-BMT relapse could achieve CR; he had DLT, which is another alternative. Remission duration of this patient after DLT was longer than the first remission duration.

The FLAG-IDA regimen was used in Philadelphia chromosome positive relapsed ALL to induce a second remission followed by BMT or PBSCT. In this series, two of eight patients received second transplants from their original donors with no further conditioning[24]. This approach may be a safer procedure because our patients who had BMT from unrelated donors in their third and fourth remission could not tolerate the conditioning CT.

In relapsed patients this regimen may be administered if there is an available donor. It seems that stem cell rescue is necessary in heavily pretreated patients who have recurrent relapses or had a previous BMT procedure. In addition, patients stand the risk of another relapse while the search for a matched related donor is undertaken.

Costs of FLAG-IDA courses were very high. Besides hematopoietic growth factors, blood products and therapy of major bacterial and fungal infections increased the cost.

In conclusion, FLAG-IDA is a very intensified therapy causing prolonged neutropenia. Its major toxicity is fatal infections in previously heavily treated patients. We could not evaluate the remission-inducing effect because many courses resulted in fatal infections before marrow recovery. We consider it not to be a cost effective therapy in a developing country. New studies with dose modifications or with FLAG may be tried as pre-BMT CT in relapsed leukemia in children. Our results were disappointing although patients carried very poor risk criteria.

REFERENCES

1. Gaynon PS, QU RP, Chappell RJ, et al. Survival after relapse in childhood acute lymphoblastic leukemia. Impact of site and time to first relapse- the Children's Cancer Group Experience.Cancer 1998; 82: 1327-1395.
2. Sica S, Salutari P, Di Mario A, D'Onofrio G, Etuk B, Leone G. Aggressive chemotherapy for acute leukemia relapsed after transplantation. Leuk Lymphoma 1994; 15: 131-134.
3. Fleischhack G, Graf N, Hasan C, et al. FLAG-IDA (idarubicin, fludarabine, high dosage cytarabine and G-CSF) an effective therapy regimen in treatment of recurrent acute myelocytic leukemia in children and adolescents. Initial results of a pilot study. Klin Padiatr 1996; 208: 229-235.
4. Steinmetz HT, Staib P, Glashmacher A, et al. Phase II study of idarubicin, fludarabine, Ara-C and G-CSF (FLAG-IDA) for treatment of refractory, relapsed or secondary acute myeloid leukemia (abstract no 821). Br J Haematol 1996; 93 (Suppl): 219.
5. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for treatment of poor risk myelodysplastic syndromes and acute myeloid leukemia. Br J Hematol 1997; 99: 939-944.
6. 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: 303-312.
7. Monitillo M, Tedeschi A, Centurioni R, Leoni P. Treatment of relapsed adult acute lymphoblastic leukemia with fludarabine and cytosine arabinoside followed by granulocyte colony-stimulating factor (FLAG-GCSF). Leuk Lymphoma 1997; 25: 279-583.
8. 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.
9. Gandhi V, Estey E, Keating MJ, Plunket W. Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy. J Clin Oncol 1993; 11: 116-124.
10. Ohno R, Tomonaga M, Kobayashi T, et al. Effect of granulocyte colony-stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia. N Engl J Med 1990; 323: 871-877.
11. Koistinen P, Wang C, Yang GS, et al. OCI/AML-4 an acute myeloblastic leukemia cell line: regulation and response to cytosine arabinoside. Leukemia 1991; 5: 704-711.
12. Tafuri A, Andreff M. Kinetic rationale for cytokine-induced recruitment of myeloblastic leukemia followed by cycle-specific chemotherapy in vitro. Leukemia 1994; 8: 2076-2082.
13. Chen ZM, Colombo T, Conforti L, et al. Effects on three new antracyclines and doxorubicin on the rat isolated heart. J Pharmacy Pharmacol 1987; 39: 947-950.
14. Dinndorf PA, Avramis VI, Wiersma S, et al. Phase I/II study of idarubicin given with continuous infusion fludarabine followed by continuous infusion cytarabine in children with acute leukemia: a report from the Children's Cancer Group. J Clin Oncol 1997; 15: 2780-2785.
15. Leahey A, Kelly K, Rorke LB, Lange B. A phase I/II study of idarubicin (Ida) with continuous infusion fludarabine (F-ara-A) and cytarabine (ara-C) for refractory or recurrent pediatric acute myeloid leukemia (AML). J Ped Hem Oncol 1997; 19: 304-308.
16. Fleischhack G, Hasan C, Graf N, et al. FLAG-IDA (idarubicin, fludarabine, cytarabine, G-CSF) in effective remission-induction therapy for poor prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experience of a phase II trial. Br J Haematol 1998; 102: 647-655.
17. Wheeler K, Richard S, Bailey C, et al. Comparison of bone marrow transplant and chemotherapy for relapsed childhood acute lymphoblastic leukemia: the MRC UKALL X experience. Br J Haematol 1998; 101: 94-103.
18. McCarthy AJ, Pitcher LA, Hann IM, Oakhill A. FLAG (fludarabine, high-dose cytarabine and G-CSF) for refractory and high-risk relapsed acute leukemia in children. Med Pediatr Oncol 1999; 32: 411-415.
19. Anderlini P, Luna M, Kantarjian HM, et al. Cause of initial remission induction failure in patients with acute myeloid leukemia and myelodysplastic syndrome. Leukemia 1996; 10: 600-608.
20. Goodman ER, Fiedor PS, Fein S, Athan E Hardy MA. Fludarabine phosphate: a DNA synthesis inhibitor with potent immunosuppressor activity and minimal clinical toxicity. Am J Surg 1996; 62: 435-442.

21. Steuber CP, Krischer J, Holbrook T, et al. Therapy of refractory or recurrent childhood acute myeloid leukemia using amsacrine and etoposide with or without azacitidine: a Pediatric Oncology Group randomized phase II study. J Clin Oncol 1996; 14: 1521-1525.

22. Spinolo JA, Yau JC, Scott E, et al. Second bone marrow transplants for relapsed leukemia. Cancer 1992; 69: 405-409.

23. Bosi A, Bacci S, Miniero R, et al. Second allogeneic bone marrow transplantation in acute leukemia: a multicenter study from the Gruppo Italiano Trapianto Di Midallo Osseo (GITMO) Leukemia 1997; 11: 420-424.

24. 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: 1137-1143.