original paper
Haematologica 1997; 82:664-667

A SINGLE HIGH DOSE OF IDARUBICIN COMBINED WITH HIGH-DOSE ARA-C (MSKCC ALL-3 PROTOCOL) IN ADULT AND PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA. EXPERIENCE AT THE UNIVERSITY "LA SAPIENZA" OF ROME

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ABSTRACT

Background and Objective. The anthracycline analogue idarubicin, either alone or in combination with other antineoplastic drugs, has shown antileukemic activity in relapsed and refractory acute lymphoblastic leukemia (ALL). In an attempt to minimize the non-hematologic toxicity and obtain a potent antileukemic effect, MSKCC activated a pilot study in previously treated adult ALL, using HD-ARA-C combined with idarubicin administered as a single high-dose infusion. We herein report our experience with a series of pediatric and adult high risk ALL and NHL patients treated with the protocol above, which confirms its feasibility, response rate and individual compliance.

Methods. In a clinical phase II study, the combination of a single high dose (HD) of idarubicin and HD cytosine-arabinoside (ARA-C), as designed at the *Memorial Sloan Kettering Cancer Center,* was applied to 70 adults and children with refractory or early relapse acute lymphoblastic leukemia (ALL) and T-cell lymphoblastic non-Hodgkin's lymphoma (NHL). Therapy consisted of HD-ARA-C 3 g/m^2/d on days 1-5, idarubicin 40 mg/m^2 on day 3, prophylactic intrathecal methotrexate on days 1 and 4, and G-CSF 5 mg/kg/d s.c. from day 7 to hematopoietic reconstitution (PMN >0.5×10^9/L).

Results. Fifty-five of the 70 patients (78%) achieved complete remission (CR), four died in aplasia due to infection and 11 were non-responders. Recovery of blood counts occurred at a median of 21 days from the start of treatment. Non-hematologic side effects were extremely limited and consisted predominantly of infections.

Interpretation and Conclusions. In view of the highly unfavorable series of patients selected, this study confirms the feasibility and antileukemic activity of the HD-idarubicin + HD- ARA-C combination in patients with refractory and early relapse ALL and NHL. The excellent tolerance to this regimen does not preclude bone marrow trasplantation as post-remission treatment.

Key words: acute lymphoblastic leukemia, chemotherapy, cytosine arabinoside, idarubicin, relapse

The anthracycline analog idarubicin, either alone or in combination with other antineoplastic drugs, has shown antileukemic activity in relapsed and refractory acute lymphoblastic leukemia (ALL). Three previous Italian multicenter studies (ALL R85; ALL R87; ALL R93) used standard dose idarubicin, administered daily or every other day, in association with intermediate or high dose (HD) cytosine-arabinoside (ARA-C) as reinduction therapy for relapsed or refractory adult and pediatric ALL patients.[1,2] In our experience, these combinations showed antileukemic activity, but caused severe gastrointestinal toxicity frequently associated to serious and persistent infections. At the Memorial Sloan Kettering Cancer Center (MSKCC), New York, idarubicin has been used as once a week treatment or in continuous infusion in adult relapse ALL.[3] Both protocols showed significant mucosal toxicity (limiting dose intensity) suggesting that protracted low level exposure to idarubicin may contribute to mucosal toxicity. Idarubicinol, the active metabolite of idarubicin, in fact has a very long half-life (> 48 hours).

In an attempt to minimize the non-hematologic toxicity and obtain a potent antileukemic effect, MSKCC activated a pilot study in previously treated adult ALL, using HD-ARA-C combined with idarubicin administered as a single high dose infusion. A phase I study with an escalating dose of idarubicin was first carried out to determine the phase II dose. An idarubicin dose of 40 mg/m^2 was well tolerated and effective in relapsed and refractory adult ALL patients.[4]

We herein report our experience with a series of

◊*This paper also appeared in the Haematologica supplement to issue n. 5, 1997 (symposium supplement).*
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Acknowledgements: this work was supported by CNR (Consiglio Nazionale delle Ricerche), Progetto Finalizzato "ACRO", contract N° 95.00450.PF39, Rome. Idarubicin was generously supplied by Pharmacia, Milan.
Received September 5, 1997; accepted September 29, 1997.

pediatric and adult high risk ALL and NHL patients treated with the protocol above, which confirms its feasibility, response rate and individual compliance.

Patients and Methods

The current series includes patients with refractory or early relapse ALL. Patients with lymphoid blastic crisis (BC) of chronic myelogenous leukemia (CML) and hematological relapse of T-lymphoblastic non-Hodgkin's lymphoma (NHL) were also included. Patients were elegible for this regimen when the following pre-requisites were fulfilled: 1) age under 60 years; 2) non-mature B-ALL; 3) primary resistance ALL to intensive first line treatment (AIEOP-BFM as a therapy for children, GIMEMA-5-drug induction for adults); 4) early first ALL or T-lymphoblastic NHL hematological relapse (adults: first remission < 24 months; children: first remission < 30 months); 5) second or subsequent hematologic relapse; 6) lymphoid BC of CML.

Prior to therapy, patients gave their consent after having been advised about the investigational nature of the study, and of the potential risks.

The protocol (Figure 1) consisted of ARA-C 3 g/m^2/d intravenously (i.v.) over a 3 hour infusion for five days, idarubicin 40 mg/m^2 i.v. at day 3 and prophylactic intrathecal methotrexate (MTX dose per age) at day 1 and 4. G-CSF (Lenograstim) was subcutaneously (s.c.) administered at the dose of 5 mg/kg/d starting on day 7 (48 hrs after the last dose of ARA-C) and continuing until the granulocyte count exceeded 0.5×10^9/L for two consecutive days. Prednisone was also given at a dose of 0.5 mg/kg/d during treatment. For the prophylaxis of HD-ARA-C-induced photophobia and conjunctivitis, all patients received glucocorticoid eyedrops every 8 hours starting before the first dose and continuing for 48 hrs after the last dose of HD-ARA-C.

Post-remission therapy was not planned, but nonetheless, allogeneic bone marrow transplant (BMT) from an HLA identical sibling or an unrelated volunteer donor or with umbilical cord blood stem cells was mandatory in responsive patients. Toxicity was defined according to the World Health Organization (WHO) grading system.[5] Evaluation of the antileukemic efficacy was based on CALGB criteria.[6,7]

Results

From January 1995 to April 1997, 70 patients (47 males and 23 females) were enrolled in this study. Their pre-therapeutic characteristics are summarized in Table 1. Forty-four patients were children (age < 15 years) and 26 were adults (age > 15 years). The immunophenotype was of B-cell lineage in 43, of T-cell lineage in 19 and hybrid (My+) in 8. Fifty-one patients were in first bone marrow relapse and eight were in second bone marrow relapse; 10 were refractory to intensive first line therapy and 1 patient presented a lymphoid BC of CML. The median duration of initial remission for patients treated in first relapse was 11 months (3-30 months). All 44 children had received standard first line treatment according to the AIEOP 88-91-95 BFM-like protocols,[8] consisting of an 8-week induction with prednisone, vincristine (VCR), daunorubicin and L-asparaginase for the first 4 weeks followed by cyclophosphamide, ARA-C and 6-mercaptopurine (6-MP) for the subsequent 4 weeks. Induction was followed by 9 courses of multidrug

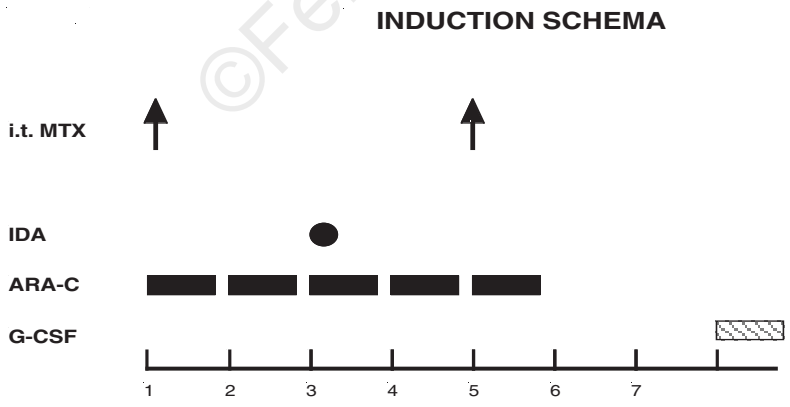

Figure 1. MSKCC ALL-3 protocol: induction schema.

chemotherapy (including HD-MTX, ARA-C and L-asparaginase) for high risk patients (9 children) and by HD-MTX consolidation, VCR, adriamycin, dexamethasone reinduction and standard MTX, 6-MP maintenance for standard risk patients (6 children). One child treated for his second relapse was reinduced with 2 blocks of the BFM-REZ 85 protocol[9] and a weekly standard dose of idarubicin and VCR. Front-line therapy for the 26 adult patients was as follows: the GIMEMA 0288 protocol[10,11] in 3; the GIMEMA 0394 pilot protocol[12] (8-week induction: standard dose ARA-C, etoposide, idarubicin combination followed by dexamethasone, VCR, L-asparaginase) in 12; Verona ALL protocol (high-dose anthracyclin) in 3; Stanford or LSA2-L2 protocols in 6 cases initially diagnosed as T-lymphoblastic NHL and hydroxyurea plus interferon-α in the patient with BC-CML.

Fifty-five of the 70 patients (78%) achieved complete remission (CR). In 11 non-responders (16%), leukemia recovered after marrow aplasia; four patients died during the aplastic phase from sepsis. Thirty-seven of the 44 children achieved CR (84%), while 18 of the 26 adults (69%) were complete responders (Table 2).

Treatment induced profound myelosuppression in all patients; G-CSF was administered to all patients, as planned. The median time to granulocytes > 0.5×10^9/L and to thrombocytes > 50×10^9/L was 17 days (8-36 days) and 22 days (5-41 days) from the start of treatment, respectively.

A summary of the extra-hematological side effects is reported in Table 3. Infection was the most frequent complication; twenty grade III-IV infective episodes were observed. Forty-eight febrile episodes occurred during neutropenia: bacterial infections were documented in 36 cases (12 sepsis; 4 fatal) and fungal infections in 8 (1 sepsis). Twelve patients experienced gastrointestinal toxicity including oral mucositis and diarrhea (WHO ≥ II). No severe cardiac events were observed after one induction cycle; one heavily pre-treated child experienced a dilatative miocardiopathy which precluded a post-remission bone marrow transplant following a second identical induction course, administered as a post-remission phase. No therapy-related pulmonary toxicity was observed. A transient cerebellar toxicity was observed in one child a few days after high-dose ARA-C infusion.

Forty-nine of the 55 responders are evaluable for the follow-up. Three patients died in CR from infections; 2 withdrew due to consolidation therapy-related toxicity; 12 relapsed at a median time of 4 months and 32 were considered eligible for bone marrow transplant. Twenty-one underwent an allogeneic BMT (10 from an HLA identical sibling, 4 from an unrelated donor and 7 with umbilical cord blood cells) and 3 received autologous BMT. Sixteen transplanted patients are currently living in CR with a median time from transplant of 7 months (range 3-12 months); one died from transplant-related toxicity and 7 relapsed at a median of 6 months from transplant.

The other 8 responding patients received different chemotherapeutic maintenance treatments: four patients are in CR and in a waiting list for an unrelated BMT; four relapsed at a median time of 6 months while the search for an unrelated volunteer bone marrow donor was still ongoing.

Table 1. Patients' characteristics.

	Total	*Age < 15 yrs*	*Age > 15 yrs*
No. of patients	70	44	26
Sex: M/F	47/23	29/15	18/8
Age			
median (years)	10	4.11	20
range	0.10-44	0.10-15	15.5-44
Phenotype			
B-lineage (Ph+)	43 (5)	31 (2)	12 (3)
T-lineage	19	9	10
Hybrid	8	4	4
Disease status			
primary refractory	10	4	6
2nd relapse	8	6	2
1st relapse	52	34	18
Previous treatments			
BFM-like protocols	42	42	-
GIMEMA 0394	12	-	12
GIMEMA 0288	3	-	3
GIMEMA "Verona"	5	2	3
"Stanford" - LSA_2-L_2	6	-	6
Others	2	-	2

Table 2. Induction results.

	Total	*Age < 15 yrs*	*Age > 15 yrs*
Number of patients	70	44	26
Complete Remissions	55 (78%)	37 (84%)	18 (69%)
Induction deaths	4 (6%)	3	1
Resistants	11 (16%)	4	7

Table 3. Extrahematologic toxicity.

	WHO=3	*WHO=4*
Oral mucositis	5	2
Diarrhea	6	3
Hepatic	3	2
Cardiac	1	0
Neurologic	1	–
Renal	3	–

Discussion

The efficacy of idarubicin associated to HD-ARA-C has been demonstrated in high risk ALL patients[1,2,3,13] and previously reported in this journal.[14,15] In the previous Italian multicenter experience, the two drugs were utilized in combination, at different doses, and in timing of administration, as reinduction therapy in refractory or relapse ALL (ALL-R-85, -87, -93 protocols). ARA-C was given at high/intermediate dose (3 g/m^2/12 hrs or 1 g/m^2/d x 6 doses) and idarubicin was administered following ARA-C infusion at a standard dose (12 or 10 or 5 mg/m^2/d), either daily or every other day. The ALL-R-85 and -87 studies included both children and adults with pretreated ALL, while in the ALL-R-93 protocol, only children were enrolled. A total of 88, 147 and 80 patients, respectively, were treated with these three regimens. The combination of ARA-C and idarubicin showed antileukemic efficacy in all three protocols with CR rates of 59, 66 and 84%, respectively. Children had a better induction response as compared to adults, with CR rates ranging between 68 and 84% compared to 54-55% for adults. However, in all three studies, gastrointestinal toxicity with mucositis and diarrhea, associated to serious bacterial and fungal infections, was the main side effect. Most of the complete responders suffered from severe or persistent infections, precluding further intensive post-remisson treament. Only 40-50% of responders resulted elegible for BMT. Similar observations on idarubicin + HD-ARA-C efficacy and toxicity have been witnessed at MSKCC in adult pretreated ALL patients.[3] With the aim of minimizing the extra-hematological toxicity, the current MSKCC (ALL-3) protocol uses HD-ARA-C combined with idarubicin administered as a single high dose (40 mg/m^2) in pretreated adult ALL.[4]

In agreement with MSKCC investigators, we applied the ALL-3 induction regimen to our high-risk ALL patients including adults and children. Seventy patients were treated and 55 (78%) achieved CR. The protocol was restricted exclusively to patients who were refractory to intensive first-line therapy, or to patients who were heavily pretreated and relapsed after a very brief initial remission (median CR length 11 months). Taking these prerequisites into account, which led to the selection of a highly unfavorable group of ALL, the CR rate of 78% clearly indicates the high efficacy of the HD-idarubicin and HD-ARA-C regimen. These data can be compared with our previous trials, using the HD-ARA-C and idarubicin combination; again, children had a significantly better induction response compared to adults: 84% and 69%, respectively. Despite the intensive previous therapy, including drugs administered at high doses, the extra-hematological side effects were acceptable. Infection was the most frequent complication, occurring in 44 cases; gastrointestinal toxicity was less frequent but severe, compared to that observed in the previous Italian multicenter studies. The majority of evaluable responder patients (32/49) were considered eligible for aggressive post-remission management, including allogeneic BMT.

The feasibility and efficacy of this regimen suggest its application in cooperative studies for the treatment of adults and children with refractory and relapse ALL. A multicenter study is necessary to delineate the incidence and duration of response.

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