Phase I trial with escalating doses of idarubicin and multidrug resistance reversal by short-course cyclosporin A, sequential high-dose cytosine arabinoside, and granulocyte colony-stimulating factor for adult patients with refractory acute leukemia

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Background and Objectives. Patients with refractory acute myeloid or lymphoid leukemia (AML, ALL) were treated with a high-dose regimen comprising idarubicin (IDR) plus short-course cyclosporin A (CsA) as multidrug resistance type-1 (MDR1) blocking agent. The principal aim was to define the maximum tolerated dose (MTD) of IDR, which is reported to be a less MDR1-sensitive anthracycline. The short CsA infusion was patterned after the results of a previous *in vitro* study.

Design and Methods. This was a phase I trial, in which eligible patients received high-dose cytarabine (HDAC) 3 g/m^2/bd on days 1, 2 and 8, 9, and IDR 12.5-20 mg/m^2/d on days 3 and 10, with increments of 2.5 mg/m^2/d from the baseline per treatment group. Intravenous CsA infusion started 4 hours before IDR and lasted 12 hours. Recombinant granulocyte colony-stimulating factor (G-CSF) was added from day 11. IDR MTD was evaluated through analysis of regimen-related toxicity (RRT).

Results. Eighteen patients were treated (16 AML, 2 ALL; MDR1$^+$: 8/8 studied). Overall response rate was 61%. Toxicity was severe but manageable up to an IDR dose of 17.5 mg/m^2/d, while grade 4 RRT developed with IDR 20 mg/m^2/d. High-grade toxicity, not strictly regimen-related, was sometimes observed at lower IDR concentrations in patients with unresolved complications from prior extensive treatments. In keeping, the complete response (CR) rate was 92% (11/12) for patients with an ECOG performance score <2 compared to 0% (0/6) in the others (p=0.000). Apart from that, induction of markedly hypocellular, leukemia-free bone marrow on day 11 was associated with achievement of CR (13 evaluable: CR 8/10 vs 0/3, p=0.035).

Interpretation and Conclusions. IDR at 17.5 mg/m^2/d (×2) can be associated with short-course CsA and HDAC for the management of refractory acute leukemias. While this regimen could deserve testing in a larger phase II trial, to document activity in MDR1+ disease, it remains important to select the most suitable patients in order to avoid the occurrence of life-threatening cumulative toxicity.

Key words: refractory acute leukemia, multidrug resistance, idarubicin, cyclosporin

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Refractory states of acute leukemia of both myeloid and lymphoid cell lineage (AML, ALL) include primary resistance to induction chemotherapy, early relapse, and second or subsequent relapse.[1,2] In this condition the effectiveness of major antileukemic compounds, i.e. the anthracycline antibiotics and high-dose cytarabine (HDAC), is greatly decreased. Anthracyclines are substrates to multidrug resistance (MDR) mechanisms associated with relapsing or refractory acute leukemia, namely MDR1 (MDR type-1 or P-gp), MRP (MDR-related protein), LRP (lung resistance protein) and BCRP (breast cancer resistance protein).[3-7]

Because a combination of anthracycline-type drugs plus HDAC is still the cornerstone of many retreatment strategies, overcoming MDR would appear a logical therapeutic step. Given the high prevalence of the MDR1 system in refractory AML, both its inhibition by cyclosporin A (CsA) or other similar drugs[8-15] and/or the use of the less MDR1-sensitive anthracyclines (idarubicin, IDR; annamycin)[16-20] have been considered. However, the use

of IDR together with CsA administered as a continuous infusion over four consecutive days has resulted in prohibitive systemic toxicity that negatively affected outcome, imposed IDR dose reduction, and prevented an association with HDAC.[21,22]

In an *in vitro* study conducted with therapeutic drug concentrations,[23] CsA-related incremental effects on IDR intracellular accumulation and cytotoxicity toward MDR1$^+$ blast cells were both dose-dependent as well as detectable after 30' incubation with CsA. IDR is highly lipophilic and this may account for both rapid cellular uptake and reduced MDR1 sensitivity.[17,19] A phase I trial to determine the maximum tolerated dose of IDR administered together with short-course CsA and sequential HDAC was designed to study dose-dependence in patients with refractory acute leukemia.

Design and Methods

Patients, diagnosis and expression of multidrug resistance

Patients with a diagnosis of refractory AML and ALL and with a life expectancy >3 months were eligible for the study, provided they gave informed consent. Refractoriness was defined by primary resistance to the current induction regimen (one-two courses) or a different salvage regimen; first relapse after a complete remission lasting <6 months; first relapse after a remission lasting >6 months if prior treatment included an allogeneic hematopoietic cell transplant (allo-BMT) or other high-dose therapy (HDAC or autograft regimen); and any subsequent relapse.[24]

The expression of MDR-associated proteins was investigated on purified blast cell samples (minimum content 90%) obtained after Ficoll centrifugation. The cytometry study employed JSB-1, MRK16, MRPm6 and LRP-56 monoclonal antibodies (all from Kamiya Biomedical Co., Seattle, WA, USA). Functional drug efflux was assessed using the $DiOC_2$ assay.[6] All results were analyzed by means of Kolgomorov-Smirnov (K-S) statistics and expressed as D values, comparing the fluorescence intensity of blast cells incubated with monoclonal antibodies to MDR proteins or with negative isotype control antibody, and $DiOC_2$ retention rates in blast cells prior to and after exposure to CsA at 2000 ng/mL for 90', respectively. Significant K-S D values were ≥ 0.15.

Treatment

Following recommendations from the German AML Cooperative Group,[25] HDAC 3 g/m^2 was administered i.v. over 3 hours twice daily on days 1-2 and 8-9 (along with corticosteroid eye drops every 4-6 hours). Instead, IDR was given i.v. on days 3 and 10 together with CsA. The daily IDR dose was increased from 12.5 mg/m^2/d to 20 mg/m^2/d in subsequent patient cohorts, with increments of 2.5 mg/m^2/d. IDR was delivered over 30' 4 hours after starting CsA. The 12 hour CsA infusion[23] was adapted from a published schedule,[13] to obtain a CsA plasma concentration >2,000 ng/mL; this concentration appears able to inhibit the MDR1 function *in vivo*. The CsA loading dose was 6 mg/kg i.v. over 1 hour, followed by 7.5 mg/kg over the subsequent 11 hours. One hour before the CsA load, patients were given dexamethasone (8 mg), clorphenamine (4 mg), and lorazepam (1 mg). Recombinant human G-CSF 5 μg/kg/d was administered subcutaneously from day 11 until the neutrophil count exceeded 1.5×10^9/L. Planned post-remission treatment aimed to deliver an identical or reduced-intensity cycle followed by an allogeneic hematopoietic stem cell transplant (allo-HSCT) from an HLA-matched donor (family-related or unrelated) or alternatively an autograft.

Study design and evaluation of toxicity

This study aimed to evaluate IDR maximum tolerated dose (MTD) as well as, preliminarily, the therapeutic efficacy of the regimen. To this end groups of 3 patients were planned to enter subsequent IDR dose levels. Because broad selection criteria led to enrollment of some very ill patients with unresolved complications from prior treatments, the accrual of additional cases to the same IDR dose level was felt necessary, up to a total of six patients, in order to distinguish between true *de novo* regimen-related toxicity (RRT) and worsening of pre-existing complications. IDR MTD was defined by the higher dose level reached before the first observed episode of grade 4 extra-hematologic RRT, at which point the phase I trial was closed. Reversible extrahematologic grade 3 and hematologic grade 4 RRTs (lasting a maximum of 4 weeks for neutrophils and 6 weeks for platelets) were accepted in view of the extremely poor prognosis of these patients. RRT was graded according to common toxicity criteria (CTC).

Evaluation of response and definitions

Bone marrow morphology was checked on day 11 (BMd11) to assess the early clearance of blast cells. A complete remission (CR) was defined by a bone marrow aspirate obtained on day 28 or later with <5% blast cells and normal trilineage hematopoiesis, with untransfused hemoglobin >9 g/dL,

Table 1. Pretreatment characteristics of patients with refractory acute leukemia.

Case no.	Age, sex	ECOG	Diagnosis[1]	MDR profile[2]	Status of disease	Treatments[3]	Prior remission
1	41, F	1	M5, del11(p14)	n/a	2nd relapse	ICE, HDT, CHAM	1 m.
2	46, F	1	M2	MDR1, MRP, LRP	1st relapse	ICE	3.3 mos.
3	38, M	3	M1	MDR1, MRP, LRP	Refractory	ICE, CHAM	–
4	63, F	2	M2, -5	n/a	1st relapse	MEC, HDT	9 mos.
5	17, F	1	M6+MDS	n/a	Refractory	ICE	–
6	39, M	1	M5	MDR1, LRP	Refractory	ICE	–
7	56, M	2	M2, inv(16)	n/a	2nd relapse	ICE, HDT, CHAM	15 mos.
8	58, M	2	M1	n/a	1st relapse	ICE	3.5 mos.
9	52, M	1	M6+MDS	n/a	Refractory	ICE	–
10	31, M	2	M2	MDR1, MRP, LRP	Refractory	ICE, allo-BMT	–
11	47, M	2	L2, C+, t(9;22)	n/a	1st relapse	08/96, allo-BMT	6 mos.
12	19, M	1	L2, C+	MDR1, MRP, LRP	1st relapse	GIMEMA, HDT	9 mos.
13	28, M	1	M4	MDR1, MRP, LRP	Refractory	ICE	–
14	28, M	1	M4	n/a	1st relapse	ICE, HDT	5 mos.
15	28, M	1	M5, abn(5)	MDR1, MRP, LRP, efflux	Refractory	ICE	–
16	34, M	1	M1	n/a	Refractory	ICE	–
17	26, F	1	M1	n/a	Refractory	ICE	–
18	59, M	1	M1, –7, t(9;22)	MDR1, MRP, LRP, efflux	Refractory	ICE, STI571	–

[1]According to FAB criteria and cytogenetics (when available); MDS denotes history of myelodysplastic syndrome; C+ denotes commom pre-B phenotype; [2]denotes positivity of MDR antigen expression and efflux test (both with K-S D value >0.15); n/a, not available; [3]ICE, idarubicin-cytarabine-etoposide; HDT, high-dose therapy with high-dose cytarabine or autograft program; CHAM, carboplatin-intermediate-dose cytarabine-mitoxantrone; MEC, mitoxantrone-etoposide-cytarabine; allo-BMT, allogeneic hematopoietic stem cell transplantation; 08/96 and GIMEMA were current protocols for adult ALL.

platelets >50×10⁹/L and neutrophils >1×10⁹/L, the response lasting for a minimum of four weeks. Patients with a 50% or greater reduction in marrow blast cell content were said to have achieved a partial response (PR) and those obtaining less than a PR were non-responders (NR). An early death (ED) was defined as death due to pancytopenic complications before hematologic response could be assessed. The patient's performance status was evaluated on day 1 of treatment according to the ECOG scale. The definitions of overall survival (OS) and disease-free survival (DFS) concerned the intervals between date of enrollment to death and date of CR to subsequent relapse or death in remission, respectively. Results in different treatment or prognostic groups were compared using the χ^2 test with Yate's corrections.

Results

Patients

Eighteen patients were treated between May 1998 and August 1999 (Table 1). The patients' median age was 39 years and the range was 17-63. MDR protein expression could be studied in only 8 patients, all of whom were MDR1⁺ (and two efflux+). Most patients were severely neutropenic (median and range: 0.5 and 0-10 ×10⁹/L) and thrombocytopenic (median and range: 28 and 6-86 ×10⁹/L), and some displayed very high-risk clinical features: case #2 (extensive fungal pneumonia), case #3 (active infection, very poor performance status), case #4 (>60-year old, poor performance status), case #7 (acute liver failure at first relapse, diabetes mellitus, serious parodontopathy), case #8 (very poor physical condition, associated central nervous system relapse), cases #10 and 11 (early relapse after allograft).

RRT and IDR MTD

The number of patients treated at each IDR dose level and related RRT patterns are shown in Table 2. Overall, twelve patients were treated at the two lower IDR concentrations, according to the study design and in view of the toxicity from associated clinical problems. Among the patients receiving IDR 12.5 mg/m²/d, severe toxicity was observed in two (cases #3, 4), however as aggravation of pre-existing complications rather than *de novo* RRT. With a total of six patients accrued to this IDR dose level, no other episode of grade 4 RRT was recorded. The subsequent cohort of six patients received IDR 15 mg/m²/d. Four patients, all with extremely poor pre-

Table 2. Analysis of hematologic and extrahematologic RRT (no. of episodes observed) and CsA levels (ng/mL, median and range; CsA1 = 4 hours from start of infusion; CsA2 = end of infusion).

IDR dose (mg/m²/d × 2):	12.5			15			17.5			20		
No. of patients	6			6			4			2		
Cases no.	1-6			7-12			13-16			17, 18		
Extrahematologic RRT, grade:	<3	3	4	<3	3	4	<3	3	4	<3	3	4
metabolic	2	0	0	3	2	0	3	0	0	2	0	0
hepatic	3	2	1[4]	2	2	2[7,11]	3	1	0	1	0	1
renal	1	0	0	2	1	0	1	0	0	0	0	0
gastrointestinal	1	2	0	2	3	1[10]	1	1	0	1	0	1
cardiovascular	0	1	0	0	0	0	0	0	0	0	0	0
neurologic	1	0	0	0	1	0	1	0	0	0	2	0
cutaneous	1	0	0	0	0	0	1	0	0	1	0	0
infectious	3	1	1[3]	1	2	3[7,8,11]	3	1	0	1	0	0
Hematologic RRT												
neutropenia <0.5×10⁹/L (days)	22 (9-30)			24 (11-26)			26 (24-32)			21, 27		
thrombocytopenia <20×10⁹/L (days)	36 (14-47)			26 (11-38)			26 (23-30)			30, 32		
red cell transfusions (days given)	4 (2-8)			6 (1-14)			4 (4-6)			4, 16		
platelet transfusions (days given)	8 (4-25)			10 (6-12)			7 (4-11)			7, 15		
CsA1	2353 (1548-2785)			2873 (2101-3905)			2473 (2060-2782)			2735, 2772		
CsA2	1982 (1315-2731)			2628 (1652-2910)			1667 (1510-1781)			1825, 2107		

Ref. [3,4,7,8,10,11] denote cases developing grade 4 toxicity that was only partially related to retreatment regimen (see Table 1 and text for details).

treatment characteristics, died early of cerebral bleeding and soft tissue infection of head and neck (cases #8 and #7, respectively), or developed high-grade complications (cases #10 and 11), again without meeting the criteria set for the definition of true grade 4 RRT and study termination. Four more cases, all with an ECOG performance score <2 and no active pretreatment complications, received IDR 17.5 mg/m²/d, and none of them suffered from dose-limiting toxicity. Lastly, two patients received IDR 20 mg/m²/d. Since one of them (case #18) developed gastrointestinal and hepatic grade 4 RRT, the MTD IDR was set at 17.5 mg/m²/d and the phase I trial was closed.

Altogether, myelosuppression was observed to be reversible, with an overall median duration of granulocytopenia <0.5×10⁹/L of 24 days and of thrombocytopenia <20×10⁹/L of 29 days. CsA plasma concentrations indicated that, at time of IDR administration, levels were always >1,500 ng/mL and almost always >2,000 ng/mL. No serious acute side effect was recorded during CsA infusion. A common symptom was a transient hyperbilirubinemia, observed in nearly all cases, independently of IDR dose. No case suffered from CsA-related nephrotoxicity or neurotoxicity.

Clinical outcome and prognostic determinants

A CR was achieved in 11 patients (61%), and a PR in 3. Clinical outcome in relation to IDR dose is summarized in Table 3. The CR rate was 50% compared to 83% in patients receiving IDR 12.5-15 mg/m²/d and 17.5-20 mg/m²/d, respectively (non-significant *p* value because of the small number of patients). A good ECOG performance score and early clearance of marrow blast cells on BMd11 were the only significant prognostic factors for CR. With regard to ECOG score (< 2 vs ≥ 2), CR rate was 11/12 (92%) compared to 0/6 (p=0.000), respectively. BMd11 results were evaluable in 13 patients; CR rate was 80% (8/10) in those with cleared BMd11, compared to zero in those with residual blast cells (p=0.035). A CR was achieved in all 8 patients with an ECOG score <2 and clear BMd11. With regard to MDR-associated proteins, no difference could be ascertained because too few cases were studied. A CR was achieved in one (case #18) of 2 patients with a positive dye efflux test.

Post-remission courses with the assigned IDR dose were given to 6 patients. Subsequently, two patients were autografted and three were allografted from matched unrelated donors. Only the latter remain alive and well 20+ months after CR. The median DFS duration was 3.9 months (range 1.2-26.7+), and median OS was 7.6 months (11.1 months for CR patients).

Discussion

Adult patients with refractory acute leukemia have a poor outlook with short median survival unless a new remission is obtained and an allo-

Table 3. Retreatment results by IDR dosing.

IDR dose (mg/m²/d×2)	*No. of patients (Case no.)*	*CR*	*PR*	*ED*	*NR*
12.5	6 (1-6)	4	1	1	–
15	6 (7-12)	2	1	3	–
17.5	4 (13-16)	3	1	–	–
20	2 (17, 18)	2	–	–	–
Total	18	11	3	4	0

HSCT is carried out promptly. Although many such patients could now be offered the procedure, mainly because of an increasing number of unrelated volunteer donors, response to salvage therapy remains a major limitation to improved survival. One effective combination has been s-HAI, comprising IDR plus sequential HDAC with or without additional fludarabine, to overcome HDAC resistance.[25] With s-HAI, 45% of 66 patients with refractory and relapsed AML achieved a CR while 32% were fully resistant.

Using the s-HAI regimen[25] as a reference model, we considered a concurrent downmodulation of MDR1 by CsA. MDR1 could be overexpressed in several cases of refractory acute leukemia, as it appears responsible for many treatment failures in large clinical series,[3,5,6] and was detectable in all the eight cases we could study. Although an association of IDR and CsA (given as a prolonged 3-6 days infusion) has been previously tested,[21,22] the reported toxicity led to reduction of IDR dosing and/or early termination of the trial. Differing from these studies, we adopted a much shorter CsA schedule (12 hours on days of IDR administration only), derived from a prior *in vitro* study,[23] featuring an association with the less MDR1-sensitive anthracycline and HDAC, which remains a pivotal drug of the whole retreatment policy, and tried to define IDR MTD in a phase I trial.

The clinical sample size was relatively small, yet adequate for this type of trial as well as representative of refractory acute leukemias according to current definitions.[1,2,24,25] Because this was a dose-finding study, the patients were carefully evaluated as regarded ECOG performance status and other factors predisposing to dose-limiting toxicities. Higher age, poor performance and cumulative residual toxicity from prior extensive treatments are frequent features of these patients, being the result of a negative prognostic selection associated with the development of refractory disease, and may sometimes account for an aggravation towards RRT rather than for a *de novo* onset of grade 4 RRT. This concept was fundamental to the conduction and interpretation of the present study, in which a pejorative clinico-prognostic profile was found to affect, totally by chance and outside patient selection criteria, 6/12 patients in the IDR <17.5 mg/m²/d groups as opposed to none in the IDR 17.5-20 mg/m²/d groups. Although these very poor risk patients were not excluded *a priori* from the trial, the data analysis indicated this treatment to be applicable and safe up to the stated IDR MTD (17.5 mg/m²/d) only to patients with an adequate performance status, without serious comorbidity, uninfected, and aged <60 years.

The overall results (CR 61%), mostly obtained with an IDR dose >15 mg/m² particularly in the group with an ECOG performance score <2 and cleared BMd11 (CR 8/8), would suggest a powerful activity of the regimen in these patients, whereas cases at higher risk for the characteristics cited should be treated differently. The use of G-CSF, compared with the German s-HAI study without G-CSF, seemingly contributed to reduce myelotoxicity from 32 to 24 median days of absolute severe granulocytopenia. In the end, IDR MTD with CsA was only 12.5% less than in the German protocol and another phase I trial in refractory ALL,[26] but equal to or higher than the dose employed with longer CsA infusions.[21,22] We have investigated a new association between IDR, short-course CsA, sequential HDAC and G-CSF in patients with refractory acute leukemia expressing (or not) MDR1, establishing IDR MTD. Despite the persisting debate on the true clinical significance of MDR1 and the best way to deal with it,[27-29] it appears desirable, for both IDR and CsA, to identify optimal administration schedules and dose-limiting toxicities, particularly in association with HDAC. The regimen described could be evaluable in a larger phase II study, to assess its activity further in MDR1⁺ leukemias.

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RB, study design and manuscript preparation; TL, GB, BC, AR, MB, AR, PV, TB, authorship according to the Vancouver definition with emphasis on the following: data handling (TL), laboratory studies (GB, BC), patient management (AR, MB, AR, PV), final approval (TB). All medical and non-medical members of the Hematology Division at Bergamo Hospi-

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Disclosures

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received November 6, 2001; accepted January 24, 2002.

What is already known on this topic

Downregulation of multidrug resistanc mechanisms including MDR1 may be an important therapeutic development to treat high-risk acute leukemia. The availability of different MDR1 inhibitors and different anthracycline-type drugs calls for phase I/II clinical trials in order to identify active and applicable drugs plus inhibitor combinations.

What this study adds

This study defines through a phase I design a cyclocsporin-idarubicin combination that can be used in association with high-dose cytarabine. High efficacy towards MDR1+ blast cells is expected, in view of idarubicin's reduced MDR1 sensitivity and further potentiation by cyclosporin.

Potential implications for clinical practice

This chemotherapeutic regimen might be employed in high-risk acute leukemias expressing MDR1 phenotype.

Mario Cazzola, Editor-in-Chief