



A new combination of carboplatin, high-dose cytarabine and cross-over mitoxantrone or idarubicin for refractory and relapsed acute myeloid leukemia

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ABSTRACT

Background and Objective. High-dose cytarabine (HiDAC) and new anthracycline-type drugs (mitoxantrone, idarubicin) are the mainstay of several active regimens against relapsed and refractory acute myeloid leukemia (AML). The present study was undertaken to assess the feasibility, toxicity, and antileukemic activity of carboplatin (CBDCA) added to a combination of the two former agents.

Design and Methods. Two regimens (R) of CBDCA plus HiDAC and either mitoxantrone or idarubicin (crossover) were sequentially evaluated. R-1 consisted of CBDCA 300 mg/m²/d (24-hour infusion) on days 1-4, HiDAC 1 g/m²/bd on days 1-5, and mitoxantrone/idarubicin 12/6 mg/m²/d on days 1-3, followed by granulocyte colony-stimulating factor (G-CSF). R-2, an attenuated-toxicity regimen, consisted of CBDCA and G-CSF as above, HiDAC on alternate days (1, 3, 5), and mitoxantrone/idarubicin 8/5 mg/m²/dose. Intended post-remission therapy included a similar, lower intensity course and a myeloablative phase supported by an allogeneic or autologous blood cell transplant.

Results. Twenty-nine patients (median age 53 years, one child) formed the study group: 10 (34%) had a primary refractory disease (8 to idarubicin-cytarabine-etoposide, ICE), 6 (21%) were at second or subsequent relapse, and 5 (17%) had a first remission lasting < 12 months. In addition, 4 patients (14%) had received prior HiDAC and 10 (34%) were relapsing after a bone marrow/blood cell transplant. Twelve patients were treated with R-1 and 17 with R-2. The complete response rate was 25% with R-1 and 53% with R-2, due to a significantly lower death rate by pancytopenic complications ($p=0.023$). The probability of response by risk class was: primary refractory 30% (43% with R-2), > 2nd relapse 33% (50% with R-2), 1st relapse < 12 months 40% (50% with R-2), 1st relapse > 12 months 50% (75% with R-2), prior HiDAC 75%, and prior transplant 30% (33% with R-2). Seven patients could undergo an autologous ($n=5$) or allogeneic ($n=2$) bone marrow/peripheral blood cell transplant after one consolidation cycle. Overall survival was 4.2 months, significantly longer in responders (complete and partial: median 11 months) than non-responders ($p < 0.001$). Median duration of complete remission was 10 months

and 2-year probability 0.31, but no patient remained disease-free at 3 years.

Interpretation and Conclusions. R-2 was well tolerated, exerted a significant activity in high-risk AML, and is amenable to further improvements. However, the lack of long-term disease-free survivors indicates the need for innovative post-remission strategies. ©1998, Ferrata Storti Foundation

Key words: refractory AML, carboplatin, high-dose treatments, blood cell autograft

Patients with acute myeloid leukemia (AML) failing induction chemotherapy, suffering from relapse within 1 year from first complete remission (CR), or at second/subsequent relapse qualify for refractory disease not curable by conventional treatments.^{1,2} Apart from that, primary refractoriness to new induction schemes as those containing idarubicin and/or etoposide or a recurrence after high-dose cytarabine (HiDAC) and/or autologous or allogeneic hematopoietic cell transplants are expected to render salvage more difficult.

Mitoxantrone, idarubicin, etoposide, HiDAC, here defined as 1-3 g/m²/dose twice daily for 4-6 days, and combinations thereof are all variously effective in refractory AML.^{2,3} Carboplatin (CBDCA) given by continuous infusion is strongly myelotoxic and was proved active, the results of CBDCA regimens varying greatly in function of patient selection criteria, drug dosage, schedule, and association with other drugs.⁴⁻⁷

We adopted a combination of CBDCA plus HiDAC and either mitoxantrone or idarubicin, the latter in a crossover design with the drug used first in a group of adult patients with refractory and relapsed AML. It is worth mentioning that the majority of our patients had received prior regimens including idarubicin-etoposide, HiDAC, and transplant. Our goal was first to obtain a response and, secondly, to administer aggressive chemo(radio)-therapy supported by an autologous or allogeneic hematopoietic stem cell graft. CBDCA, HiDAC, and anthracyclines have different mechanisms of action and are therefore expected to be partially noncross-resistant. Etoposide was not included because a topoisomerase II inhibitor,

such as mitoxantrone or idarubicin, was already administered to most patients and maybe redundant with HiDAC.⁸ We present the clinical outcome of 29 patients with high-risk AML who were treated with two different-intensity CBDCA-based regimens.

Materials and Methods

CBDCA-based regimens

Regimen 1 (R-1) consisted of CBDCA 300 mg/m²/d as 24-hour continuous infusion on days 1-4, HiDAC 1 g/m²/12-hourly on days 1-5, mitoxantrone/idarubicin 12/6 mg/m²/d on days 1-3. Patients previously treated with adriamycin or idarubicin received mitoxantrone, and *vice versa* in a crossover design. Patients previously exposed to both drug types received mitoxantrone once more. R-1 was followed by subcutaneous 5 µg/kg/d granulocyte colony-stimulating factor (G-CSF, from Hoffman-LA Roche or Dompè-Biotec, Italy), starting from day 6 and until the peripheral absolute neutrophil count was $>1.5 \times 10^9/L$ after the leukocytic nadir. A reduced intensity regimen (R-2) was introduced after the evaluation of treatment results and toxicities with R-1 in the first patient cohort (see below for details). R-2 consisted of unmodified CBDCA and G-CSF; HiDAC was delivered on alternate days and mitoxantrone/idarubicin concentration was slightly reduced (Figure 1). Cases achieving a complete response were to be consolidated with an intermediate-intensity cycle (Figure 1) and considered eligible to autologous or allogeneic marrow/blood cell transplant. Collection of peripheral blood CD34⁺ cells for autograft was attempted after the consolidation course. Prophylactic measures during reinduction therapy were hyperhydration to maintain an adequate urine output, oral ciprofloxacin 500 mg/bd, and transfusions with packed red cells and multiple donor platelets for hemoglobin < 8 g/dL and thrombocytopenia $< 20 \times 10^9/L$, respectively.

Definitions and statistics

Refractory AML was defined as primary resistance to induction course(s), relapse within 12 months from first CR, and any subsequent relapse.^{1,2} Recurrent AML was defined as first bone marrow recurrence >12 months from first CR.

Achievement of CR, in patients transfusion-free and with $>1.5 \times 10^9/L$ neutrophils and $>100 \times 10^9/L$ platelets, required the disappearance from the bone marrow of recognizable leukemic cells with evidence of normal trilineage hematopoiesis. A partial response (PR) was defined as the persistence of 25% or less marrow blast cells, and no response $>25\%$ blast cells. A subsequent relapse was diagnosed by the detection of 5% or greater bone marrow blast cells.

Comparison between different prognostic and treatment groups were by means of the chi-squared test with Yate's correction, the Student's t-test, and the log-rank test. Survival and remission estimates were produced by Kaplan-Meier analysis.

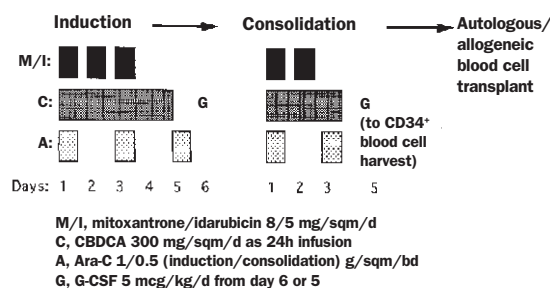


Figure 1. CBDCA-based regimen 2 (R-2).

Results

Patients entered on trial from June 1994-March 1997 were refractory to or relapsing after front-line or salvage regimens. Front-line adult regimens were with adriamycin-cytarabine-thioguanine or, since January 1994, with idarubicin-cytarabine-etoposide (ICE), plus either HiDAC or autologous bone marrow/blood cell transplantation (ABMT/ABCT) consolidation, the preparative regimens for autografts being with HiDAC/total body irradiation (TBI: 12 Gy over 3 days). Elderly AML patients and adult relapse or refractory states before the present study were managed with a mitoxantrone-cytarabine-etoposide combination followed by high-dose consolidation if possible.

Twenty-one patients with refractory AML according to the definition given^{1,2} and 8 additional patients with recurrent AML formed the study group. The median observational time since diagnosis of refractory/relapsed AML to data analysis (July 1997) was 31 months (range 4 months-3.5 years). The main diagnostic characteristics of patients, their prior treatments and the distribution of risk features by retreatment protocol, are illustrated in Table 1. There was a single pediatric case, and 5 patients were > 60 year-old. Early relapses occurred after 4.5-11.2 months. Five of 8 patients relapsing after 12 months of first CR (12.6-37.7 months) had a recurrence following an ABMT/ABCT, 2 after HiDAC-based consolidation, and only one (aged 62 years) after conventional post-remission treatment. Thus, only one out of 29 total patients (3.4%) did not have a refractory AML or high-dose treatments prior to receiving the CBDCA-based regimen. All patients had been previously treated with one or more anthracycline-type drug and 83% with etoposide. One refractory patient had an acute myeloblastic transformation of a Philadelphia-positive chronic myelogenous leukemia proved resistant to four courses with daunorubicin-thioguanine-cytarabine, and another patient, aged 64, was refractory to mitoxantrone-cytarabine-etoposide. The other 8 primary refractory patients had not responded to one (n=6) or 2 (n=2) induction ICE courses.

Outcome

The first 12 patients received R-1, an highly toxic schedule that was abandoned in favor of R-2. Two R-

Table 1. Patient characteristics by regimen.

Clinical and pre-treatment features	Total (n=29)	R-1 (n=12)	R-2 (n=17)
Age (yr), median (range)	53 (5-67)	46 (26-67)	54 (5-64)
Gender, M:F (no.)	12:17	4:8	8:9
FAB class, M0:1:2:4:5 (no.)	2:11:8:4:4	2:5:2:2:1	0:6:6:2:3
Blast count $\times 10^9/L$, median (range)	0.30 (0-146)	0.37 (0-146)	0.22 (0-61.3)
Prior treatments			
MIT:IDA:DNR:ADR,* no.	11:13:2:7	6:2:2:6	5:11:0:1
Etoposide, no.	24 (83%)	8	16
HiDAC, ^o no.	4 (14%)	3	1
Allogeneic BMT, no.	1 (3.4%)	1	0
ABMT/ABCT, no.	5/4 (31%)	3/0	2/4
Disease status			
Primary refractory, no.	10 [#] (34%)	3 (25%)	7 (41%)
1st relapse <12 mos., no.	7 (24%)	1 (8%)	6 (35%)
≥ 2 nd relapse, no.	6 (21%)	4 (33%)	2 (12%)
1st relapse >12 mos., no.	8 (27%)	4 (33%)	4 (23%)

*MIT, mitoxantrone; IDA, idarubicin; DNR, daunorubicin; ADR, adriamycin; ^ooutside a transplant procedure; [#]eight pts refractory to ICE: idarubicin 10 mg/m²/d on days 1-3, etoposide 100 mg/m²/d on days 1-5, cytarabine 100 mg/m²/bd on days 1-7, and G-CSF 5 μ g/kg/d from day 8 to neutrophil recovery.

1 patients died of septic complications caused by ciprofloxacin-resistant strains of *Pseudomonas spp.* and *Enterococcus*, respectively. With R-2 the CR rate increased from 25% to 53% (6/13 or 46% in refractory AML and 3/4 or 75% in relapsed AML) and the incidence of toxic side effects and early deaths was reduced. Overall and comparative treatment outcome by regimen and by risk factors is detailed in Table 2. All CRs were obtained after a single chemotherapy course. CR plus PR rates were superimposable with either mitoxantrone (9/20, 45%) or idarubicin (4/9, 44%). The analysis of responses indicated some prognostic trends, albeit in very small patient subgroups. Of 8 patients resistant to the current front-line ICE protocol, two received R-1 and died of pancytopenic complications; 6 received R-2: two entered a CR (33%) and four proved resistant. The CR rate among patients recurring after a transplant was 30% (3/10), 33% (2/6) when the transplant was a first-line procedure, and 50% (2/4) with R-2 regardless time to develop the recurrence.

Toxicity

Myelotoxicity was severe with both regimens, with a median absolute neutropenic period in excess of two weeks despite additional G-CSF (Table 3). In contrast, gastrointestinal tract and mucosal toxicity was much milder with R-2, so that these patients

Table 2. Outcome to reinduction therapy by treatment regimen, risk factors, and prior high-dose treatments.

	Total (n=29)	R-1 (n=12)	R-2 (n=17)
CR, no.	12 (41%)	3 (25%)	9 (53%)
PR, no.	3 (10%)	1 (8%)	2 (12%)
Resistant, no.	5 (17%)	1 (8%)	4 (23%)
Pancytopenic death, no.	9 (35%)	7 (58%)	2 (12%)*
CR by risk category			
Primary refractory (n=10)	3 (30%)	0/3	3/7 (43%)
1st relapse <12 mos. (n=5)	2 (40%)	0/1	2/4 (50%)
≥ 2 nd relapse (n=6)	2 (33%)	1/4 (25%)	1/2 (50%)
1st relapse >12 mos. (n=8)	4 (50%)	1/4 (25%)	3/4 (75%)
CR by prior high-dose consolidation			
With transplants (n=10)	3 (30%)	1/4 (25%)	2/6 (33%)
With HiDAC (n=4)	3 (75%)	2/3 (66%)	1/1

* $p=0.023$.

were less prone to develop infectious complications (35% vs. 100%, with many R-1 patients suffering from multiple infectious episodes). Severe metabolic, renal, neurologic, and auditory toxicities were not observed.

Post-remission therapy

Two of 3 PR patients received no further therapy because of prolonged pancytopenia and progressive disease, respectively, and one underwent a second allogeneic peripheral blood transplantation after high-dose busulphan-melphalan conditioning. The patient achieved a CR but then died of sepsis and severe chronic graft-versus-host disease. Of 12 CR patients, one died early of uncontrolled fungal infection and one >60 year-old was given no further therapy. Ten patients received the consolidation course and 7 had autologous CD34⁺ cells collected ($1-4.3 \times 10^9/kg$ CD34⁺ cells). One CR patient underwent an allogeneic blood cell transplantation, complicated by a delayed platelet recovery and a fatal bleeding, and 4 stopped treatment because of poor performance status/advanced age (n=2) or inability to collect CD34⁺ cells (n=1). In the fourth case, a search for an unrelated bone marrow donor was initiated. Five patients (age 44-62 years, 2 refractory and 3 relapsed) were autografted after high-dose BCNU-etoposide-cytarabine-melphalan (n=3) or HiDAC/TBI (n=2) combinations. Time from CR to autograft was 1.5-5.8 months (median 3.3). The neutrophil count was $>0.5 \times 10^9/L$ after 8-20 days (median 12) from transplant. Time to reconstitute a spontaneous platelet count $>20 \times 10^9/L$ ranged from 18-91 days (median 30).

Table 3. Comparative toxicities of CBDCA-based regimens.

Parameters	R-1 (n=12)	R-2 (n=17)	p value
Neutrophils < 0.5x10 ⁹ /L, days	18 (9-36+)	20 (10-45+)	ns
Platelets < 20x10 ⁹ /L, days	19 (9-36+)	22 (9-38)	ns
GI toxicity,* no.	7 (58%)	2 (12%)	p=0.023
Fever > 38°C, days	6 (0-10)	4 (0-12)	ns
Cumulative infections, no.	17	6 (35%)	p=0.0016
Pneumonia, no.	8 (66%)	4 (23%)	p=0.052
Sepsis, no.	9 (75%)	2 (12%)	p=0.0022

*Grade III-IV gastrointestinal toxicity according to WHO scale; ns for values not < 0.05.

Remission and survival duration

Median CR duration was 10 months and 2-year probability was 0.31. Duration of response was increased in patients with recurrent (n=5) rather than refractory AML (n=7): median and 2-year probability 2.5 years and 0.53 vs 0.8 years and 0.17, respectively (non-significant p value). The length of disease-free interval was seemingly affected by the intensity of postremission therapy including transplants, since less intensively treated patients appeared to experience shorter disease-free intervals (Table 4). However no patient experienced a disease-free interval longer than 3 years. Cumulative CR and overall survival estimates are displayed in Figure 2a. Median overall survival from entry into study was 4.2 months but responders lived significantly longer (complete plus partial: median 11 months, 2-year probability 0.38) than nonresponders, whose median survival was less than one month (p<0.001 by the log-rank test, Figure 2b).

Discussion

The results of this trial suggest CBDCA can be associated with HiDAC and other drugs for the management of refractory and relapsed AML of adults, that dosage and scheduling of CBDCA and associated drugs must be defined carefully, and that patients previously given idarubicin and etoposide-containing induction regimen or HiDAC consolidation courses with or without transplants (ABMT/ABCT or allografts) may represent a peculiar high-risk category owing to selection of AML cell clones resistant to the new drugs and the reduced clinical tolerance after transplants.

We considered CBDCA because noncross-resistant with both topoisomerase-II inhibitors and HiDAC, and insensitive to type 1 multidrug resistance (MDR-1) mechanism, which is often overexpressed in recurrent and refractory AML.^{9,10} Because other molecular drug transporters, DNA repair and glutathione-S-transferase systems can counterbalance this property and lead to CBDCA resistance,¹¹ we avoided using CBDCA alone.

Table 4. Post-remission treatment realization and outcome.

Post-remission therapy	No. of patients	CR duration (months)	Notes
None	2	0.5, 6	1 pt. died of infection, 1 pt. > 60 yr
Consolidation only	4	3, 4+, 4+, 10	1 pt > 60 yr, 2 pts. poor performance, 1 pt.: search unrelated donor
Consolidation + allograft	1	14	Pt. died of bleeding
Consolidation + autograft	5	5, 11, 12+, 30, 35	
Allograft*	1	27	Pt. died of sepsis and GVHD

*PR patient achieving CR at transplant.

Prior phase I/II studies demonstrated cumulative CBDCA not exceeding 1500 mg/m² over five consecutive days to be both safe and relatively effective, while higher concentrations were associated with worse toxicity and those < 1000 mg/m² or < 300 mg/m²/d gave lower response rates.^{13,14} In refractory AML, CR rates with CBDCA alone were < 10%,^{4,15} 10-20%,¹⁶ >20%.^{13,14,17} However, the best results were reported in patients who had not been intensively pretreated. The synergistic cytotoxicity described *in vitro* with some drugs, including cytarabine and mitoxantrone,¹⁸ led to combinations with etoposide (CR 0%, 40%),^{4,7} anthracyclines (CR 26-33%)^{19,20} and ara-C (CR 27-50%).^{6,21-23}

According to these data, the cumulative 1200 mg/m² CBDCA dosage we adopted for R-1 appeared rational but, to be preserved in R-2, it required a further reduction of HiDAC and mitoxantrone/idarubicin concentrations in order to limit regimen-related toxicity. The alternate-day HiDAC schedule was derived from a Cancer and Leukemia Group B (CALGB) post-remission consolidation trial,²⁴ where it reduced toxicity compared with daily administration. Even if the sensitivity to HiDAC may be reduced in refractory patients and the activity of 1 g/m² dose is presumably different from 3 g/m²/dose, we introduce the lower intensity schema not to alter the CBDCA dosage. Mitoxantrone and idarubicin are both active drugs for refractory leukemias^{2,3} and were suitable for a crossover design based on prior treatments given to the patients.

Eventually, the 53% CR rate obtained with R-2 was remarkably similar to the results reported with other recent investigational programs, such as FLAG/FLANG (fludarabine, HiDAC, G-CSF/FLAG plus mitoxantrone) and HAM/sequential HAM (HiDAC and mitoxantrone).²⁵⁻²⁸ The median response duration of 10 months compares well with data from HAM and sequential HAM (4.5 months and 4 months)^{25,26} and FLAG/FLANG (6/8 months).^{27,28} We noted an inferior outcome in patients resistant to ICE or relapsing after

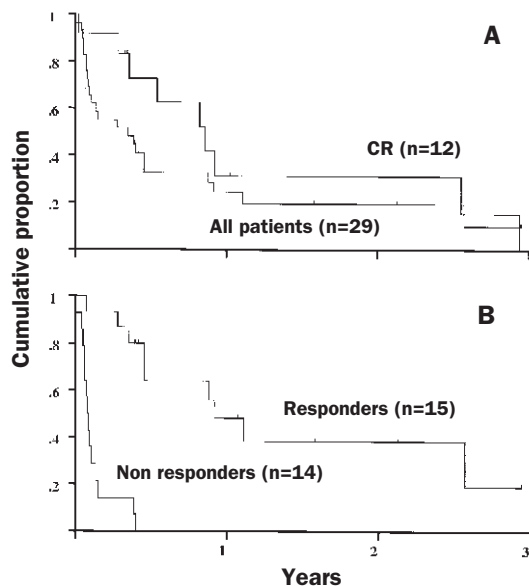


Figure 2. Cumulative results of R-1 and R-2 for relapsed and refractory AML: A. actuarial durability of CR (12 patients) and overall survival (29 patients); B. survival of responders (CR+PR, 15 patients) vs nonresponders (14 patients).

a transplant in first CR (CR: 33%). Patients with primary refractory disease after one course of standard chemotherapy, that is with daunorubicin and conventional-dose cytarabine, have a CR probability of 34-38%,^{29,30} which is higher (CR 56%) if retreatment cycle includes mitoxantrone/HiDAC.²⁹ The lower response rate we obtained may thus reflect the selection of a worse patient population resistant to ICE, by inference with the trials supporting the superiority of idarubicin and the benefits from additional etoposide in first remission AML.³¹ In ICE-resistant patients, the FLAG combination was reported highly effective (6/8 CR, 75%), but again the patient series was small and the duration of response was very short.²⁷ The recurrence after prior HiDAC was apparently not an unfavorable prognostic sign, being associated with a CR rate of 75%, but relapse after transplants was associated with a high-risk of failure and toxic death as in other series.²⁷ Regarding nonresponders and the new schema, the refractory rate to R-2 was reasonably low (23%), but the high pancytopenic death rate observed with R-1 prevents from drawing conclusions on the whole patient series.

The analysis of long-term outcome indicated a worthwhile prolongation of disease-free survival in patients able to undergo an allogeneic/autologous bone marrow/peripheral blood transplant, but none survived disease-free > 3 years. Although a fraction of patients suffering from first late relapse after conventional treatment could achieve cure without transplants, as suggested by some recent long-term observations,^{32,33} this was not foreseeable in a series in which only one of 29 patients was in first late relapse without

prior high-dose treatments. The fact that peripheral blood CD34⁺ cells were successfully mobilized for autografting purposes by the consolidation cycle confirms that CBDCA can also be an useful mobilizing agent, but it does not appear, from the data presented, that this is associated with an improved survival compared to mafosfamide-purged autologous bone marrow transplants.³⁴ The role of peripheral blood cell autograft in second and late remission AML remains to be determined.³⁵

In conclusion, a CBDCA-based regimen (R-2) proved active in refractory and relapsed AML of adults. Although the specific contribution of CBDCA to a positive outcome cannot be ascertained, it may have been substantial in some cases since HiDAC and anthracycline (mitoxantrone or idarubicin) dosages were somewhat lower than in other recent salvage regimens,^{25,26} but results were similar. Unfortunately, because the data from FLAG/FLANG, HAM, and R-2 as rescue of primary failures to ICE or ABMT/ABCT procedures are very scanty, it is not possible to assess precisely the role of CBDCA and other drugs in these high-risk situations. As regards R-2, the regimen activity could be further increased by adopting a sequential rather than continuous drug schedule, in accordance with the sequential HAM study results,²⁵ by increasing the HiDAC dosage, or by considering the adjunct of fludarabine to potentiate HiDAC cytotoxicity.³⁶ Currently, we are adopting a sequential schedule (days 1-3 and 8-10) with HiDAC increased to 2 g/m²/dose. A major obstacle is represented by the unsatisfactory postremission therapy results. Inducing an effective graft-versus-leukemia effect³⁷ and increasing the rate of family unrelated bone marrow transplants are promising research avenues in this area.

Contributions and Acknowledgments

RB was responsible for the conception of the study, its design, direct supervision, and writing of the paper. TL was responsible for data handling. MB followed the patients clinically. GB, PB and AR were responsible of laboratory aspects related to collection/manipulation of peripheral blood cells and transplants. TB was the senior investigator responsible for the study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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