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Fractionated cyclophosphamide added to the IVAP regimen (idarubicin-vincristine-L-asparaginase-prednisone) could lower the risk of primary refractory disease in T-lineage but not B-lineage acute lymphoblastic leukemia: first results from a phase II clinical study

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ABSTRACT

Background and Objectives. **In a prior study, primary resistant acute lymphoblastic leukemia (RES-ALL) was observed in 11 of 176 (6%) adult patients treated with a four drug regimen (IVAP), its incidence being higher in T-cell or Philadelphia (Ph) chromosome/BCR-ABL rearrangement positive ALL cases with a blast cell count >25×10⁹/L (RES-ALL rate 19%, *p*=0.04). Aiming to minimize this percentage of resistant disease, fractionated cyclophosphamide (f-CY) was then added to the IVAP regimen.**

Design and Methods. **Study 08-96 was a prospective, collaborative phase II trial carried out at eight general hospital centers specialized in the care of hematologic malignancies. Historical IVAP-treated patients served as a retrospective control group. All consecutive, untreated patients (>15 years) with a diagnosis of ALL or advanced-stage lymphoblastic lymphoma (LBL) were eligible. RES-ALL was defined as the persistence of >5% ALL cells in the bone marrow 28-40 days after the start of the IVAP regimen (idarubicin 10 mg/m²/d on days 1 and 2; vincristine 2 mg on days 1, 8 and 15; L-asparaginase 6,000 U/m² on alternate days × 6 from day 8; prednisone 60 mg/m²/d on days 1-21). In the new study, two f-CY schedules were sequentially adopted: CY 150 or 75 mg/m²/bd, given for 4 consecutive days before IVAP (f-CY 1200 or 600, expressing total CY dose in mg/m²).**

Results. **Eighty-eight patients were evaluable (age range 15-74 years, blast count 0-240×10⁹/L, 14 T-lineage, 74 B-lineage, 13 Ph/BCR-ABL⁺). The first 39 patients received the f-CY 1200 schedule, 22 patients received f-CY 600, and the last 27 patients were not given any f-CY. These changes were dictated by the results of interim analyses of the f-CY groups (RES-ALL rate not reduced, myelotoxicity increased). Altogether, compared with the historical IVAP and no f-CY groups, the incidence of RES-ALL was not decreased by the addition of f-CY 1200/600 in B-lineage ALL, regardless of Ph/BCR-ABL expression and blast count. However, none of 14 T-ALL cases in the new study had RES-ALL (8 in f-CY groups, 5 of whom with >25×10⁹/L blast cells), compared to 5/39 (13%, overall) or 4/21 (19%, with >25×10⁹/L blast cells) among the control cases. Owing to small sample size, this difference was not statistically significant.**

Interpretation and Conclusions. **This preliminary experience suggests that T-ALL may be more sensitive than B-lineage ALL to an early therapy including f-CY. The hypothesis could be tested in a larger clinical trial.**

Key words: adult ALL, ALL subtypes, remission, resistance, cyclophosphamide

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Adult acute lymphoblastic leukemia (ALL) is highly responsive to combinations of vincristine (V), prednisone (P), L-asparaginase (A), and anthracyclines. A complete remission (CR) can be achieved with these regimens in the majority of cases. However, some patients manifest primary resistant disease (RES-ALL), leading to a significantly worse outlook. In large series with >100 patients, the incidence of RES-ALL was <5%,[1,2] 5-10%,[3,4] 10-15%,[5-11] and 30%,[12] indicating the need for improved induction regimens. In four recent studies, cyclophosphamide (CY) was added from as early as induction day 1 to conventional three or four drug schedules.[13-16] These new regimens were suggested to be more effective, in terms of lower primary refractory rates,[13,16] although this was not confirmed by the single phase III trial thus far performed.[15]

Between October 1991 and November 1996, we treated 176 adults with ALL using a combination of idarubicin, V, A and P (IVAP).[17] On the day of response evaluation (day 28-40), 11 patients (6%) with more than 5% residual ALL cells in the bone marrow were declared to have RES-ALL. This was an improvement over the 13% RES-ALL rate observed

with the previous adriamycin-based regimen.[6] With the IVAP induction protocol, the occurrence of RES-ALL correlated to some extent with older age and higher blast cell count (non-significant *p* values) and especially with a diagnosis of Philadelphia chromosome/BCR-ABL rearrangement-positive (Ph/BCR-ABL$^+$) and T-cell ALL (4/40 and 5/39, respectively, vs 2/97; p=0.025), particularly when the blast cell count was > 25×10^9/L (cumulative data: 7/36 vs 2/43; p=0.04). This definition of RES-ALL was clinically meaningful, since median and long-term survival rates for the 11 RES-ALL cases were only 0.7 years and 18% at 4 years, compared to 2 years and 31% at 5 years in the patients achieving CR (p<0.025).

In the new study 08-96, the administration of fractionated CY (f-CY), styled after the *hyper-C-VAD* regimen,[16] was considered as an adjunct to the IVAP protocol in order to reduce the risk of RES-ALL further, and thereby improve the long-term outcome of the entire patient population. This is the focus of the present report.

Design and Methods

Patients

All untreated patients with ALL aged 15 years and over (no upper age limit) were eligible for the study 08-96. ALL was confirmed by morphologic (French-American-British/FAB classification), histochemical and immunophenotypic studies of bone marrow blast cells. Cytogenetic and/or gene rearrangement studies (P190 and P210 BCR-ABL, ALL-1/AF4 and E2A-PBX1 transcripts) were available in most cases. Immunologic ALL subsets were T-cell ALL (myeloperoxidase-, cyCD3$^+$, CD2$^+$, CD7$^+$, CD5$^+$), early-B ALL (myeloperoxidase-, cyCD79a/CD22$^+$, CD19$^+$, CD10$^+$ or $^-$), and B-ALL (myeloperoxidase-, B-lineage markers and surface immunoglobulin expressed clonally). Patients with stage III-IV lymphoblastic lymphoma (LBL) of either B-cell or T-cell lineage were also eligible.

Remission induction regimens and management policy

Fractionation of CY over several days may increase the therapeutic index of the drug.[18] A very low RES-ALL rate was reported with the f-CY-containing *hyper-C-VAD* regimen.[16] The IVAP regimen with or without f-CY is depicted in Figure 1. Two f-CY schedules were developed sequentially in consecutive patient groups, while the last group of patients received no CY, as indicated in the Figure. The reasons for attenuating and then omitting f-CY were the unchanged RES-ALL rate and the increased marrow toxicity, especially in patients with B-lineage disease (see the *Results section* for details), as observed at interim analyses performed every 6 months during the course of the study.

CY was administered before IVAP for 4 consecutive days at a 150 and then 75 mg/m^2/dose every 12 hours (cumulative dose 1200 and 600 mg/m^2, respectively: f-CY 1200 and f-CY 600), together with P 20 mg/m^2/bd. The f-CY phase was followed by IVAP. In all programs, early central nervous system prophylaxis consisted of triple intrathecal therapy (TIT in Figure 1). Compared to the historical IVAP regimen,[17] the A dose was lowered from 10,000 U/m^2/d on days 8-14 to 6,000 U/m^2 from day 8 on alternate days × 6, in order to minimize A-related toxic side effects, frequently observed in the original IVAP study, while a third V injection was added on day 15. Supportive care policy was as in the IVAP study.[17]

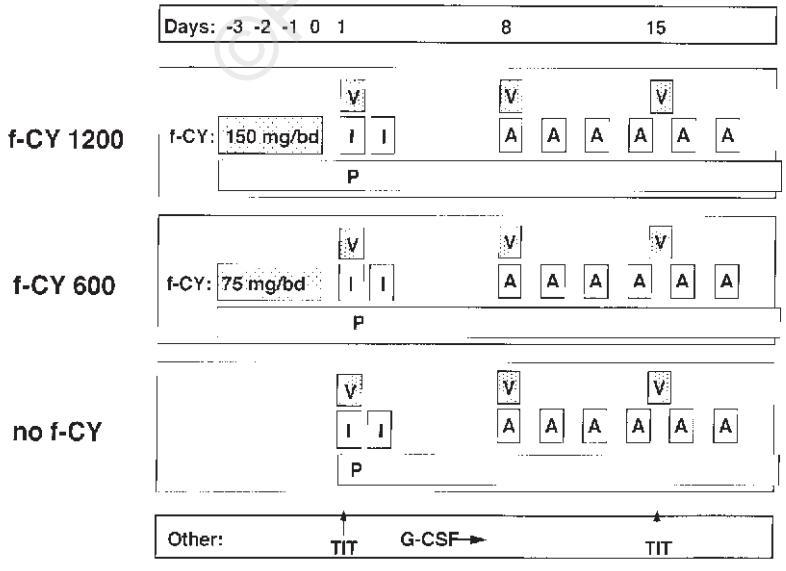

Figure 1. Schematic representation of IVAP remission induction regimen, with or without f-CY 1200/600.
Key (all drugs by i.v. route): f-CY, fractionated cyclophosphamide 150 mg/m^2/bd (f-CY 1200) or 75 mg/m^2/bd (f-CY 600) from days –3 to 0; I, idarubicin 10 mg/m^2/d on days 1 and 2; V, vincristine 2 mg on days 1, 8 and 15; A, L-asparaginase 6,000 U/m^2/d on alternate days (x6) from day 8; P, prednisone 20 mg/m^2/bd on days -3 to 0 (f-CY regimens) and 30 mg/m^2/bd on days 1-21. G-CSF, subcutaneous G-CSF 5 µg/kg/d from day 3 until a stable neutrophil count >1.5×10^9/L. TIT, triple intrathecal therapy with methotrexate 12.5 mg, cytarabine 50 mg and prednisone 40 mg.

Table 1. Patient characteristics (p=ns) and outcome (p=ns) by f-CY regimen and f-CY doses.

	f-CY 1200 n=39	*f-CY 600 n=22*	*no f-CY n=27*
Characteristics			
Age (yrs), median (range)	39 (19-74)	35 (17-58)	37 (15-65)
Sex (M/F), no.	24/15	10/12	18/9
FAB morphology (L1/L2/L3), no.	11/25/0	0/14/0	12/12/2
Blast count ($\times 10^9$/L), median (range)	8.7 (0-204)	3.4 (0-42)	1.1 (0-240)
Immunology (B/T/early B CD10$^{+/-}$), no.	0/4/20/15	0/4/14/4	2/6/15/4
Cytogenetics (Ph/BCR-ABL/other/normal), no.	6/11/14	4/2/12	3/4/14
Outcome			
CR, no.	33 (85%)	21 (95%)	22 (81%)
RES-ALL, no.	5 (13%)	0	1 (4%)
Early death, no.	1	1	4

Lymphoblastic lymphoma: 3 B-lineage in f-CY 1200 group, 1 T-lineage in no f-CY group.

Response criteria, statistics, study objectives

Bone marrow aspiration for response evaluation was performed 28 days after the start of the IVAP regimen, or later (up to day 40) as clinically indicated. RES-ALL was defined as the persistence of >5% ALL cells in the bone marrow and/or in extramedullary sites previously found to be positive. A complete remission (CR) was defined by a regenerating and normocellular bone marrow with a blast cell content <5%, with untransfused hemoglobin >100 g/L, neutrophils >1.5$\times 10^9$/L, platelets >100$\times 10^9$/L, and negative or normalized clinical findings. Statistical comparisons were made by means of the chi-squared test with Yate's correction, Student's t-test, and the log-rank test as appropriate. The incidence of RES-ALL was evaluated in the different risk categories (high-risk: Ph/BCR-ABL$^+$ ALL or T-ALL, with >25$\times 10^9$/L blast cells; low-risk: other cases) and compared between the different f-CY and historical IVAP treatment groups. Because of the risk-oriented design of postremission protocol 08-96[19] and the short follow-up of the patients, analyses of a post-remission therapy and disease-free survival were not within the objectives of this study.

Results

Patients and treatment groups

Eighty-eight patients were evaluable. The first patients were allocated to receive the f-CY 1200 regimen (n=39). A second group of patients received the attenuated f-CY 600 schedule (n=22), and eventually f-CY was omitted (n=27). The characteristics of the 3 treatment cohorts are reported in Table 1. No significant difference was noted. Four patients had a diagnosis of LBL (3 in the f-CY 1200 group and one in the no f-CY group).

Response and incidence of RES-ALL

Overall, 76/88 patients achieved a CR (86%), 6 had RES-ALL (7%) and 6 died early of complications (7%) (Table 1). In the f-CY 1200/600 groups, the CR rate was 88% (54/61) and the RES-ALL rate 8% (5/61). Compared to the results of the no f-CY group, this is not significantly different, suggesting that f-CY is not effective in reducing the RES-ALL rate. Indeed, the highest incidence of RES-ALL was noted in the more intensive f-CY 1200 group (5/39 or 13%) while no case of RES-ALL was observed in the smaller f-CY 600 group. In view of these findings, the risk factors for RES-ALL were analyzed separately and the results compared with those of the historical IVAP cohort.

Role of risk factors and comparison with historical IVAP

The analysis is illustrated in Table 2. No patient with T-ALL (n=14) had RES-ALL (8 were f-CY-treated and 6 were not). Five patients in f-CY groups had high-risk T-ALL with >25$\times 10^9$/L blast cells. The incidence of RES-ALL in the f-CY-treated cases and those treated with historical IVAP was, respectively, 0/8 (0%) vs 5/39 (13%) in unselected patients, and 0/5 (0%) vs 4/21 (19%) in high-risk cases. Neither figure was statistically significant, because of the small number of cases. In Ph/BCR-ABL$^+$ ALL (n=13), RES-ALL was noted in both low-risk and high-risk subgroups, regardless of f-CY dose and at approximately the same rate as in historical controls. In low-risk, B-lineage Ph/BCR-ABL- ALL (n=61), 3 patients treated with f-CY 1200 had RES-ALL (5%). Intermediate-risk features were present in two of them (age 61 years, blast count 100$\times 10^9$/L). Again, the incidence of RES-ALL was similar to that seen in the historical cohort. Altogether, the addition of f-CY 1200/600 to IVAP was unable to abrogate the occurrence of RES-ALL in B-lineage ALL (whether at high- or low-risk), while no case of RES-ALL has been seen in the limited number of T-ALL patients so far entered into the study.

Table 2. Comparative incidence of RES-ALL by risk factors (percentage in brackets).

Risk groups	*Total*	*Study 08-96 f-CY 1200-600*	*no f-CY*	*historical IVAP*
High-risk				
T-cell, blast count* >25	0/7	0/5	0/2	4/21 (19)
Ph/BCR-ABL+, blast count* >25	1/3 (33)	1/3 (33)	–	3/15 (20)
Low-risk				
T-cell, blast count* <25	0/7	0/3	0/4	1/18 (5)
Ph/BCR-ABL+, blast count* <25	2/10 (20)	1/7 (14)	1/3 (33)	1/25 (4)
B-lineage, Ph/BCR-ABL–	3/61 (5)	3/43 (7)	0/18	2/95 (2)

*$\times 10^9$/L.

Table 3. Comparative toxicity (number of events if not differently stated).

	f-CY 1200 n=39	*f-CY 600 n=22*	*no f-CY n=27*
Hematologic			
Time to CR (days), median (range)	28 (20-40)	27 (20-37)	22 (14-39)*
Neutrophils <0.5×10^9/L (days), median (range)	13 (1-29)	17 (8-31)	12 (0-40)
Neutrophils <0.5×10^9/L × 21 days, no.			
T-lineage	1/4	0/4	0/6
B-lineage	5/35	6/18	3/21
Infectious			
Septicemia	8	5	5
Pneumonia	3	3	6
Nervous system	2	0	1
Other/not specified	5	3	1
Other			
Metabolic/hepatic	5	5	5
Gastrointestinal	6	1	1
Neurologic	2	2	5
Other (lung/heart/kidney)	3 (1/1/1)	0	0

*p=0.0003 vs f-CY group.

Toxicity

The toxic side-effects of IVAP with or without f-CY are reported in Table 3 (only toxicities of WHO grade >2 are indicated). The addition of f-CY proved to be a feasible therapeutic move, but hematologic toxicity tended to be increased. The longer time to CR reflected the delayed recovery of normal bone marrow function (see criteria for the definition of CR status). The duration of severe absolute neutropenia was only slightly increased but, with f-CY 1200/600, a neutropenic period of abnormally long duration (>21 days) was observed in about 20% of B-lineage ALL patients (14/74), as opposed into only 7% of those with T-ALL (1/14). Because there were relatively few T-ALL cases in this series, this early finding, together with the unimproved RES-ALL rate, prompted us to reduce and eventually omit the f-CY phase. In any case f-CY did not appear to have an impact on the incidence of documented infectious complications. Fatal infectious episodes developed in 4 patients in the group not treated with f-CY and in 2 in the group treated with f-CY. The fatality rate caused by early neutropenic pneumonia was high (5/12, 42%), and in 2 of these cases a fungal etiology was ascertained. These patients had remained neutropenic for 8-23 days (median 13 days). Non-hematologic and non-infectious toxicity was comparable among treatment groups, with a slightly higher prevalence in the f-CY 1200-treated patients.

Discussion

The successful management of adult ALL rests on a combination of diagnostic accuracy, adequate patient preparation, delivery of risk-adapted remission induction-consolidation therapy, and a high level of patient care. When this is fulfilled, the risk of primary resistant ALL (RES-ALL) is fairly low but not totally absent. Patients with RES-ALL have a reduced probability of survival and disease-free survival, calling for novel therapeutic approaches. In a retrospective series of 176 cases receiving the IVAP induction protocol, we found an increased risk of RES-ALL in patients with a blast cell count >25×10^9/L and either T-ALL or Ph/BCR-ABL+ ALL (19% of cases), but no other disease category was spared.

In the subsequent study 08-96, an additional, brief

course of f-CY was added to the IVAP. CY is not cross-resistant with the drugs forming the IVAP schedule and is relatively effective in untreated ALL. The reported incidence of CR with single-agent CY varied between 0% and 40%, depending on cumulative dose and schedule.[20] CY was confirmed to be active in refractory and relapse states too.[21] The importance of CY fractionation has been emphasized in highly aggressive entities such as Burkitt's lymphoma and B-ALL.[18,22] In untreated patients, CR and RES-ALL rates with CY-containing regimens were 81% and 11%,[15] 89% and 11%,[14] 85% and 7%,[13] and 95% and 1.5%,[16] respectively. While the 3 former studies adopted a single-shot schedule (day 1), the best results were those obtained with the *hyper-C-VAD* regimen employing CY 300 mg/m^2 every 12 hours for 3 days.

In view of the formerly known myelotoxicity of IVAP,[17,23] in the current study the f-CY dose was 33% lower than in the *hyper-C-VAD* regimen (total 1,200 vs 1,800 mg/m^2). Moreover, following early confirmation of an increased myelotoxicity (greater in patients with B-lineage ALL, representing 84% of all cases), a second cohort of patients received a yet further reduced dose (f-CY 600). Lastly, as preliminary study results were not showing abrogation of RES-ALL, f-CY was omitted. Although with f-CY 1200 the RES-ALL rate was 13% (5/39), the analysis of outcomes by risk factors identified an association with Ph/BCR-ABL positivity, elevated blast count and age, but not with T-cell immunophenotype. The results and hence the conclusions are not appreciably different if the 39 and 22 patients treated with f-CY 1200 and f-CY 600, respectively, are considered together and compared with the historical series and the not f-CY-treated group. It appears that f-CY did not alter the probability of RES-ALL in patients with B-lineage subset disease. The incidence of RES-ALL was higher in patients with Ph/BCR-ABL+ ALL and a blast count >25×10^9/L. An alternative induction regimen should be sought for all these patients.

The conclusion concerning T-ALL could be sensibly different, since none of five high-risk patients treated with f-CY regimens developed RES-ALL, compared to 19% of those in the historical control group. The obvious limitation of the study was the small number of patients. More T-ALL patients will have to be treated with a f-CY-containing regimen to confirm this early suggestion. The 16% incidence of T-ALL in our series is lower than that found in other unselected adult ALL series, but as yet we have no explanation for this. Apart from this, our findings are in keeping with those of other studies. In the Cancer and Leukemia Group B trial, adopting unfractionated CY on day 1 of induction therapy, the CR rate achieved in T-ALL was 97%,[13] and it was presumably that high in the *hyper-C-VAD* study reporting an overall RES-ALL rate of only 1.5%.[16] A subset analysis of the GIMEMA randomized trial is awaited with interest.[15]

Another interesting point would be to assess whether dose fractionation is as important in T-ALL as it seems to be in B-ALL.[18,22] In addition, the administration of CY later during induction or early consolidation has been associated with an improved remission duration in T-ALL.[7,24-26] With regard to the latter strategy, our results (not presented here) are encouraging.

In summary, adding two different dose levels of f-CY to IVAP proved feasible but did not decrease the risk of RES-ALL in the whole patient population. On analyzing the results separately, the RES-ALL rate was unmodified by the addition of f-CY in immature B-lineage ALL (regardless of the risk class), while no refractory case was observed in a small group of patients with T-ALL. In this respect the f-CY study was terminated too early, essentially because the overall results being accrued in a series mainly composed of B-lineage ALLs were masking a possible benefit restricted to patients with T-lineage disease. The difference between the two disease subsets was further underlined by the greater marrow tolerance to IVAP, with or without additional f-CY, demonstrated by T-ALL patients.[23] The early use of f-CY during remission chemotherapy should be investigated further in T-lineage adult ALL.

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Study design and supervision by RB and TB. Paper written by RB. Data handling by TL. EP, PF, GR, SM, PC, GL-D, MV, TI, PC and GC were involved in study design, discussion, and patient management.

Disclosures

Conflict of interest: none

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