THERAPEUTIC IMPACT OF ADULT-TYPE ACUTE LYMPHOBLASTIC LEUKEMIA REGIMENS IN B-CELL/L$_3$ ACUTE LEUKEMIA AND ADVANCED-STAGE BURKITT'S LYMPHOMA

Teresa Lerede,* Renato Bassan,* Andrea Rossi,* Eros Di Bona,° Giuseppe Rossi,# Enrico M. Pogliani,@ Teresio Motta,^ Valter Torri,§ Maurizio Buelli,* Benedetto Comotti,* Piera Viero,* Alessandro Rambaldi,* Sergio Cortelazzo,* Francesco Rodeghiero,° Tiziano Barbui*

*Hematology/Bone Marrow Transplant and ^Pathology Departments of Ospedali Riuniti di Bergamo; °Ospedale Civile di Vicenza; #Spedali Civili di Brescia; @Ospedale San Gerardo di Monza; §Istituto Ricerche Farmacologice 'M. Negri' di Milano, Italy

ABSTRACT

Background. Adult B/L$_3$-ALL is a rare disease subset characterized by an aggressive clinical course and a poor response to conventional adult ALL-type chemotherapy. Recent data from the GMALL Group showed that prognosis can be improved with an innovative treatment regimen. In the current retrospective survey we focus on therapeutic results obtained at our Institutions during a 15-year period with ALL-type regimens in 34 adults with either B/L$_3$-ALL or advanced-stage Burkitt's lymphoma.

Methods. Five successive ALL treatment programs were developed. They included a homogeneous induction phase with early intrathecal chemoprophylaxis, multidrug postremission consolidation followed by cranial irradiation (4 trials), high-dose chemotherapy plus autografting (2 trials), late consolidation (2 trials), and variable-length maintenance (4 trials). Early response and prolonged disease-free survival rates were analyzed according to selected clinical and therapeutic variables.

Results. Overall, a complete remission was achieved in 62%, with a median duration of 1.6 years and a 10-year remission rate of 49%. A diagnosis of B/L$_3$-ALL (p=0.007), the use of idarubicin instead of adriamycin during induction (p=0.018), a serum creatinine <1.6 mg/dL, and an uninvolved central nervous system were associated with higher response rates. As regards long-term disease-free survival, results were significantly better in patients with <1x10^9/L L$_3$/blast cells in the peripheral blood (p=0.0029) and/or aged <50 years (p=0.04), and in those consolidated with the most recent rotational high-dose plus peripheral blood stem cell autotransplant regimen.

Conclusions. According to the results presented, ALL-like regimens may still represent a worthwhile therapeutic choice. The use of idarubicin during induction, the prognostic subclassification of patients, a careful control of dysmetabolic complications, the selection of the proper chemo-radioprevention for meningeal disease and perhaps the introduction of high-dose chemotherapy supported by autologous stem cell rescue appear to be the mainstay of further improvements.

Key words: B-ALL, Burkitt's lymphoma, adults, treatment

A recent study from the German Multicenter acute lymphoblastic leukemia (GMALL) Group reported state-of-the-art treatment results for adult B-ALL,[1] a disease subset accounting for less than 5% of all adult ALL. With very few exceptions, B-ALL exhibits the so-called L$_3$ (Burkitt's lymphoma-like) morphology, nonrandom translocations involving chromosomes 14, 18, 2 and 8, *c-myc* gene deregulation, and a mature B-lineage phenotype with monotypic surface immunoglobulin. In the GMALL study, the remission rate and leukemia-free survival increased from 44% and 0%, obtained with ALL-type treatment, to 74% and 71% using an intensive regimen introduced for childhood B-ALL and Burkitt's lymphoma.

Similar results in adult B-ALL and Burkitt's lymphoma were reported by others with slightly different programs.[2,3] Previously, adult B/L$_3$-ALL was considered an extremely malignant condition with a high risk of early death, meningeal spread, and recurrence following adult-type ALL therapy. Trials conducted with ALL-directed chemotherapy, reviewed by Hoelzer,[1] usually involved less than 10 total patients and reported remission rates from 0-67% (median 35%) and leukemia-free survival from 0-33%. However, these conclusions were subject to bias caused by the small patient number and the facts that, rather frequently, B/L$_3$-ALL was excluded from some of the most representative adult ALL trials[4-7] and that risk factors other than B-ALL phenotype or L$_3$ morphology were not recognized.

From 1979-1995 we conducted five successive collaborative chemotherapy studies for adult ALL,[8-11] enrolling 346 total patients aged 15-78 years and including B/L$_3$-ALL as well as advanced-stage lymphoblastic and Burkitt's lymphomas. We are now able to evaluate early response rate and long-term outcome of B-ALL or Burkitt's lymphoma in 34 homogeneously treated adults. To the best of our knowledge this is the largest series of its kind to be compared with smaller ones reviewed by Hoelzer and the GMALL study results.[1] The conclusions from this survey differ sensibly from prior studies and show that, under selected circumstances, these neoplasms may be successfully managed with modern adult ALL-type schedules.

Patients and Methods

Diagnosis and inclusion criteria

B-ALL was diagnosed when > 30% bone marrow cells were lymphoid blasts expressing surface markers that indicated mature B-lineage differentiation with light chain immunoglobulin (SIg$^+$) of either the κ or λ type.[12] B cell markers used to demonstrate B-cell lineage affiliation were anti-CD19 and anti-CD20 monoclonal antibodies. An L$_3$ Burkitt-cell morphology suggestive of B-ALL according to the French-American-British subclassification[13] was not required in cases with a SIg$^+$ phenotype, but it was mandatory in those without the immunophenotype study. Cases with L$_3$ morphology and non-SIg$^+$ phenotype were excluded. Burkitt's lymphoma was diagnosed as a subtype of small noncleaved cell lymphoma.[14] Advanced stage was defined as clinical stage III/IV by the Ann Arbor[15] and the St. Jude[16] staging systems, or stage C/D according to the National Cancer Institute staging classification for Burkitt's lymphoma.[17] Lymphoma patients with bone marrow involvement had < 30% bone marrow L$_3$ cells. When staging results were discordant, the patient was included in the analysis provided advanced stage was confirmed by at least two of the three staging systems.

Patients

The study population comprised all consecutive B/L$_3$-ALL patients enrolled into prospective adult ALL trials from 1979-1995. Collaborative adult ALL studies involved at various times up to seven different hematology-oncology institutions in Northern Italy (Ospedali Riuniti di Bergamo, Ospedale Civile di Vicenza, Ospedale San Gerardo di Monza, Spedali Civili di Brescia, Istituto di Scienze Mediche Università di Milano, Istituti Ospitalieri di Cremona, Ospedale Generale di Bolzano). As of December 1995, our file contained data on 346 patients, 24 of whom met the diagnostic criteria for B/L$_3$-ALL (7% of all cases). Twenty-three cases from 4 Centers were evaluable; one patient aged 75 years with a very poor performance status received CHOP-like chemotherapy and was excluded. Patients with advanced-stage Burkitt's lymphoma observed at Bergamo Hospital during the same period were managed similarly and were thus eligible for the present review.

Treatment

Details of the adult ALL protocols in use at Bergamo and Vicenza Hospitals from 1979-1992 and from 1993 to 1995 in subsequent collaborative studies have been published.[8-11] These programs were designed for the management of adult ALL and were not specifically intended for B/L$_3$-ALL or Burkitt's lymphoma. A summary of induction and consolidation plus maintenance

Table 1. Treatment protocols (all drugs by intravenous route unless otherwise specified).

Program	Induction	Consolidation/ CNS phase	Myeloablative phase	Maintenance
HEAV'D[1]	A, V, As, P	A, V, C, it MTX, RT	–	MP, MTX, C
OPAL-HDara-C[2]	A, V, As, P	A, V, HDara-C, it MTX + ara-C	–	MP, MTX
Reinforced HEAV'D[3]	A, V, P, C	A, V, C, ara-C, T,it MTX, RT	–	MP, MTX
IVAP[4]	I, V, As, P	I, V, As, C, ara-C, T, TIT, RT	B, E, M	MP, MTX
07/93[5]	I, V, As, P	I, V, E, ara-C, C, Dx, TIT, RT	C, E, M	–

Abbreviations: A, adriamycin; V, vincristine; As, L-asparaginase; P, prednisone; C, cyclophosphamide; RT, cranial radioprophylaxis; MP, 6-mercaptopurine (po, orally); MTX, methotrexate (it, intrathecal; im, intramuscular); HD, high-dose; ara-C, cytosine arabinoside (bd, twice a day); T, teniposide; I, idarubicin; B, BCNU; E, etoposide; M, melphalan; Dx, dexamethasone; ABMT, autologous bone marrow transplantation; ABSC, autologous blood stem cell transplantation.

[1]Induction: A 30 mg/m² + V 2 mg dd 1 and 15 + As 10000 U/m²/d 1-14 + P 40 mg/m²/d until CR + it MTX 12.5 mg d 2. Postremission: A 25-40 mg/m² dd 1-3 + V 2 mg d 2 + C 500-750 mg/m² d 2 + it MTX 12.5 mg d 1 (4 courses q 21 dd); RT 24 Gy after course 2. Maintenance: MP 100 mg/d + MTX 30 mg im/week + C 300 mg po week (for 3 years).

[2]Induction: as HEAV'D. Post-remission: HDara-C 2g/m²/bd dd 1-6 (course 1); A 30 mg/m² + V 2 mg dd 1 and 15 (course 2); it MTX 12.5 mg monthly x4 and it ara-C 50 mg monthly x4 (repeat 4 times). Maintenance for 3 years.

[3]Induction: as HEAV'D (excluding As) plus C 300 mg/bd (fixed dose) dd 1 and 15. Postremission: 4 courses as HEAV'D (A 25 mg/m²/dose + C 500 mg/m²/dose); RT 24 Gy after course 4 + it ara-C 50 mg x4; T 150 mg/m² + araC 300 mg/m² x4 over 2 weeks; V 1 mg/m² + C 300 mg/m² alternating weekly with T + ara-C (x12). Maintenance for 2 years.

[4]Induction: I 10 mg/m² dd 2 and 3 + V 2 mg dd 1 and 8 + As 10,000 U/m²/d dd 8-14 + P 40 mg/m²/d until CR + G-CSF 5 µg/kg/d from d 15 or 4 until neutrophil count >1.5x10⁹/L + triple intrathecal (TIT) d 2 with it MTX 12.5 + ara-C 50 mg + P 40 mg. Postremission: I 12 mg/m² dd 1 and 3 + V 2 mg d 2 + C 500 mg/m² d 2 + As 10000 U/m² dd 5-7 + TIT d 2 + G-CSF 5 µg/kg/d from d 8 until neutrophil count >2.0x10⁹/L (4 courses q 21 dd); RT 24 Gy; B 300 mg/m² d1 + E 450 mg/m² dd 1 and 2 + M 110 mg/m² d 2 + ABMT d 4 (patients <50 years); V 1 mg/m² + C 300 mg/m² alternating weekly with T 150 mg/m² + ara-C 300 mg/m² (x12). Maintenance for 6/12 months (ABMT yes/no).

[5]Induction: as IVAP. Postremission: I 10 mg/m² d 1 + ara-C 3 g/m² d 1 + VCR 2 mg d 2 + E 450 mg/m² d 2 + Dx 4 mg bd dd 1-7 + TIT + G-CSF 5 µg/kg/d from d 3 until neutrophil count >2.0x10⁹/L (courses 1,3,5); I as above + VCR as above + C 750 mg/m² dd 1 and 2 + TIT + G-CSF as above (courses 2,4,6); RT 18 Gy after course 3 + TIT x2; C 4 g/m² d 1 + E 800 mg/m² dd 2 and 3 + M 110 mg/m² d 4 + ABSC d 6.

phases is reported in Table 1. A permanent central venous access was inserted at diagnosis in most cases and an early diagnostic lumbar puncture was performed. Daily oral allopurinol 300-600 mg/day and hyperhydration/urine alkalinization with normal saline and sodium bicarbonate were given to correct or to prevent uric acid nephropathy and kidney failure. Intravenous furosemide 20-40 mg/day was added to increase urine output whenever indicated. In the presence of a creatinine level >1.6 mg/dL or uric acid >8 mg/dL all chemotherapy was usually deferred for 24-72 hours with the exception of corticosteroids at 0.5-1 mg/kg/day. Management of anemia, neutropenia, thrombocytopenia and related complications was that adopted for ALL patients at the time of the study. To hasten neutrophil recovery after myelotoxic induction and consolidation chemotherapy, patients in IVAP and 07/93 studies received additional recombinant granulocyte colony-stimulating factor (G-CSF). Timing and dosage of G-CSF are detailed in Table 1. Prevention of neutropenic infectious complications was carried out with oral paromomycin-nystatin or ciprofloxacin-nystatin or ciprofloxacin-fluconazole.

Definitions and statistics

A complete remission (CR) was defined as the disappearance of lymphoblastic/L_3 cells from bone marrow and other involved tissues and cerebrospinal fluid upon completion of induction chemotherapy. The bone marrow had to be normocellular or moderately hypocellular with clear evidence of normal trilineage hematopoiesis, and the patient had to be discharged to home. If required, particularly in lymphoma patients, the clinical CR pattern had to be confirmed by ultrasound scan, computed tomography or nuclear magnetic resonance. A recurrence was defined as the detection of >5% SIg^+ L_3/blast cells in the bone marrow, L_3/SIg^+ blasts in the spinal fluid or biopsy proven Burkitt's lymphoma in swollen lymph nodes, bone marrow, or other clinically suspect tissues.

Comparisons of treatment outcome among different patient groups were performed by means of the Fisher exact test and the log-rank test (univariate analysis). Multivariate analysis was conducted with logistic regression analysis and the Cox proportional hazard model, using the SAS statistical package system. Survival was taken from date of diagnosis to death or last

	B/L$_3$-ALL (n=23)	Burkitt's lymphoma (n=11)	Total (n=34)	
Patients:				
Age (yr), median (range)	43 (15-65)	51 (17-70)	44 (15-70)	
M/F	15/8	9/2	24/10	
L$_3$ cells (x10^9/L), median (range)	0.9 (0-31)	0	–	
LDH (U/L), median (range)	5095 (295-19,195)	649 (366-12,280)	3540 (295-19,195)	
Creatinine >1.6 mg/dL, % cases	18	18	18	
Uric acid >8 mg/dL, % cases	63	45	54	
Extramedullary/nodal disease, (no.)				
CNS	2	2	4	
bone marrow		6		
GI tract		7		
liver		2		
kidney		1		
pleura		1		
ovary		1		
gums		1		
Treatment (no.):				
HEAV'D	7	1	8	
OPAL-HDara-C	2	–	2	
Reinforced HEAV'D	1	9	10	Table 2. Diagnostic features and treatment assignment.
IVAP	6	–	6	
07/93	7	1	8	

follow-up. Disease-free survival (DFS) was calculated from the date of CR to recurrence, death in CR from any cause, or time of last follow-up in CR. Survival and DFS estimates were calculated and plotted by the Kaplan-Meier method.

Results

Patients and treatment

The demographic and clinical features of 34 adults with B/L$_3$-ALL or Burkitt's lymphoma, and the number of patients assigned to each treatment protocol are reported in Table 2. In the B/L$_3$-ALL group, confirmation of diagnosis by immunophenotype was obtained in 18 out of 19 cases studied (one technical failure). Four of these (22%) displayed non-Burkitt (L$_2$) morphology but were nevertheless considered B-ALL because of SIg positivity. Five cases diagnosed between 1980 and 1982 could not be immunophenotyped and were included on the sole basis of L$_3$ morphology. Thus, 18 out of 23 patients (78%) were immunophenotypically SIg+ B-ALL. Stated inclusion criteria were met by 11 out of 18 patients with histologically proven Burkitt's lymphoma.

Overall results

Median follow-up for all patients from day of diagnosis do date of analysis was 4 years (range 3 months-13.1 years).

A CR was initially achieved in 21 patients (62%), while the remainder died early of refractory disease (n=6, 18%), pancytopenic complications (n=5, 15%), or kidney failure (n=2, 6%). These two uremic deaths occurred after 11 and 3 days, respectively, and were caused by an acute tumor lysis syndrome that developed in two Burkitt's lymphoma patients (aged 50 and 70 years) who had elevated serum creatinine and/or uric acid levels on presentation.

For all patients, median survival from diagnosis was 6.6 months, and projected overall survival from 4-12 years was 30% (Figure 1a); 12 patients are still living (35%). For 21 CR patients, median DFS was 1.6 years and projected DFS from 4-12 years was 49% (Figure 1a). Eleven patients are alive in first CR. One patient aged 64 years died of invasive fungal infection soon after the achievement of CR. Two CR patients had postremission treatment curtailed by toxicity problems. No patient underwent allogeneic bone marrow transplant in first CR. All six eligible patients in protocols IVAP and 07/93 received an autograft, five of them with

peripheral blood stem cells (>4×10⁶/kg CD34⁺ cells) collected after the first consolidation course of the 07/93 regimen. All five of these patients engrafted promptly and remain well and disease free at 0.5-2.5+ years.

Nine patients suffered a recurrence: 5 in the bone marrow, 1 in bone marrow plus CNS, and 3 in the CNS. Relapse occurred after a median of 4 months (range 1.2-19 months), and within 6 months in 7 out of 9 cases. Three of the four CNS relapses took place very early during remission, before prophylactic cranial irradiation was initiated. Median survival from relapse

Figure 1. Kaplan-Meier estimates of: A) overall survival (OS) and DFS of all patients; B) DFS by peripheral blood blast/L₃ cell count (< or >1x10⁹/L); C) DFS by blast count (x10⁹/L) and age (yr): Group 1, blast count < 1 and age < 50; Group 2, blast count < 1 or age < 50; Group 3, blast count > 1 and age > 50.

was only 22 days (range 4 days-1.4 years). The only patient surviving in second CR at 12+ months received an allogeneic BMT.

Prognostic variables

The data are summarized in Table 3.

As regards induction of CR, results were poorer in patients with elevated creatinine or CNS disease (nonsignificant *p* values) and with Burkitt's lymphoma. In this last case, reasons for failure were pancytopenic complications in 3 patients, uremia in 2, and refractory disease in 3. The incidence of refractory disease was lower in B/L₃-ALL, being documented in 3 out of 23 patients (13%). We also noticed that 6 of 15 evaluable patients (5 early deaths excluded) receiving adriamycin-based regimens showed primarily refractory disease (40%), as opposed to none of 12 evaluable patients (2 early deaths excluded) treated with idarubicin-based regimens. Thus the CR rate was higher with idarubicin.

As regards DFS in patients achieving remission, the only factor strongly correlated with improved outcome was a low tumor burden as shown by a peripheral blast cell count <1×10⁹/L (Figure 1b). A positive prognostic trend was also observed in the younger age group (p=0.07 by univariate analysis) and, far from any statistical significance due to the small patient number in the relative subgroups, in the lower serum LDH group and the chemotherapy program 07/93 group. In view of the results observed in different age and blast cell patient cohorts, that affected approximately an equal number of patients, we performed a joint blast cell-age prognostic analysis. Actuarial DFS was 67% for patients with < 1×10⁹/L circulating blasts and aged < 50 years, 60% for patients with a higher blast count or age, and 0% in the group of patients with both higher blast counts and age (Figure 1c). This difference was confirmed as significant by an *equality over strata* log-rank statistic.
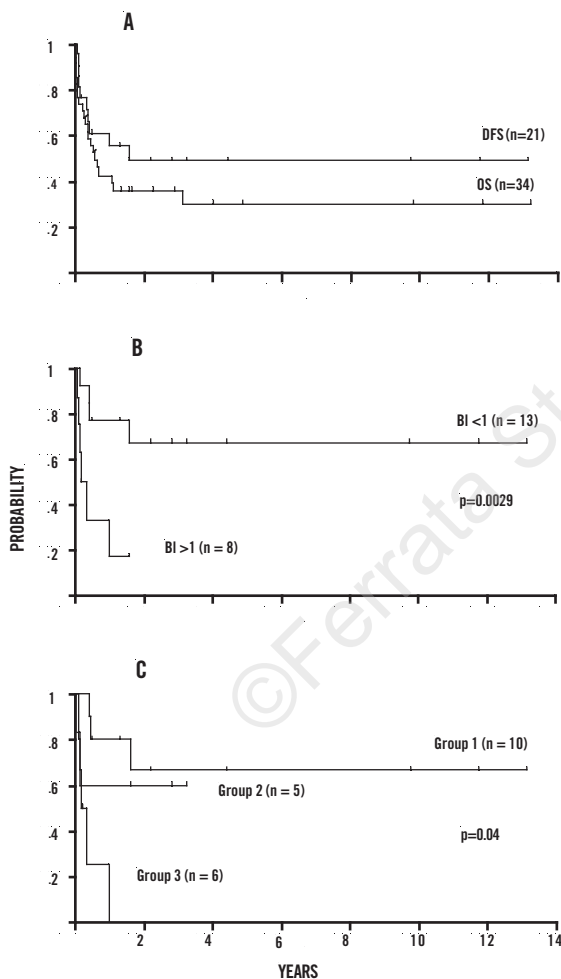
Discussion

Recent GMALL results in adult B-ALL are unprecedented and likely to remain a key reference for any future therapeutic attempt.[1]

Table 3. Therapeutic outcome by prognostic variables. CR: complete remission; DFS, disease-free survival of CR patients; OS, overall survival. Only significant p values are reported (U/V, univariate analysis; M/V, multivariate analysis).

Variable	No. of cases	CR no. (%)	DFS median (yr)	5-yr %	OS median (yr)	5-yr %
Age (yr),						
<50	20	12 (60)	NR	64	0.8	40
>50	14	9 (64)	0.33	28 (4-yr)	0.3	16 (4-yr)
L_3 cells (x10^9/L),						
<1	23	13 (56)	NR	67[1]	0.7	39
>1	11	8 (73)	0.33	17 (2-yr)	0.3	10 (2-yr)
LDH (U/L),						
<500	6	3 (50)	NR	59	1	25
>500	20	13 (65)	0.33	33	0.3	37
Creatinine (mg/dL),						
<1.6	18	12 (66)	NR	69	1.1	36[2]
>1.6	4	1 (25)	0.2	50 (1-yr)	0.1	25 (1-yr)
CNS (no.),						
negative	30	20 (67)	1.6	46	0.5	31
positive	4	1 (25)	2.8	100 (3-yr)	0.1	25 (3-yr)
Diagnosis (no.),						
B/L_3-ALL	23	18 (78)[3]	1	47	0.5	41
Burkitt's NHL	11	3 (27)	NR	67	0.3	18
Anthracycline type (no.)						
Adriamycin	20	9 (45)	NR	62	0.5	25
Idarubicin	14	12 (86)[4]	0.4	47 (3-yr)	0.5	46 (3-yr)
Treatment protocol (no.),						
07/93	8	7 (87)	NR	69 (3-yr)	NR	58 (3-yr)
Others	26	14 (54)	1	43	0.5	26

NR, not reached. [1]p=0.018 U/V; p=0.0029 M/V; [2]p<0.025 U/V; [3]p=0.005 U/V; p=0.007 M/V; [4]p=0.018 U/V.

However, the results we obtained with adult ALL-specific regimens in a relatively large patient series are generally better than those reported previously and may also contribute to clarifying the factors able to influence long-term DFS in this disease.

The median patient age in our study was higher than in Hoelzer's report (44 vs. 34 years), as was the incidence of documented CNS involvement (17% vs 12%). The number of cases with L3 morphology without an available confirmatory immunophenotype was similar (22% vs 19%). On the other hand, the peripheral blood cell count was lower (median 0.9×10^9/L vs 12.3×10^9/L), and while we referred to absolute blast cell count, the German study considered total white cell count. Because mature and immature myeloid cells are sometimes increased in the blood of B-ALL patients, who in turn are seldom neutropenic, it seems advisable to have a common modality for the correct definition of this important risk factor. Altogether, we had more patients presenting with renal failure and a 7% incidence of B/L_3-ALL among adult ALL, which is almost twice that commonly reported by others. The exact incidence of B-ALL in the GMALL report is not detailed, but it was only 2% in trial 01/81, in which 368 total cases were enrolled[18] and 9 B-ALL were treated.[1] All these data document either an augmented incidence of B/L_3-ALL in our region, or a very low exclusion rate at diagnosis, as suggested by the extended patient age range and the number of cases with renal failure included in our study.

Our therapeutic results support separate conclusions for the remission induction and postremission consolidation phases. During induction, excluding deaths due to pancytopenic complications and uremia, that are reducible only by means of improved supportive care,[19] we found that refractory disease was almost exclu-

sively associated with the use of the adriamycin regimen (30%, 9/20 patients) rather than with the idarubicin counterpart (none of 14 patients). Since other induction drugs were the same, this was quite an interesting finding even though the patient number was rather small. Idarubicin is highly active in adult ALL and different ALL subsets are known to respond heterogeneously to anthracyclines.[10,20] It may indicate that early treatment results in adult B-ALL can be improved by idarubicin through complementary mechanisms. First, idarubicin would be less vulnerable than other similar compounds to the cellular drug efflux mediated by membrane-associated P170 glycoprotein,[21] frequently expressed in B/L_3-ALL.[22] Secondly, the idarubicin alcohol metabolite, idarubicinol, is cytotoxic and exhibits a plasma half-life of > 50 hours.[23] Because B-ALL grows very rapidly, with an estimated generation time of 25 hours, and benefits greatly from drug fractionation,[24] idarubicinol might effectively inhibit cell proliferation during the 48-72 hours estimated for every B-ALL cell to transverse the cell cycle. Interestingly, GMALL induction studies employing daunorubicin confirmed a relatively high refractory rate (44% in study ALL 01/81 to 17% in study B-NHL 86, mean 25%), so that the exact place of idarubicin in B-ALL should be elucidated further by both clinical and experimental *in vitro* studies on a larger series.

Analysis of postremission treatment results showed an overall long-term DFS of 49% and, under selected circumstances, DFS rates as high as in the GMALL B-NHL 83/86 studies. Patients with a DFS of 60-67% were those presenting with a low blast count ($< 1 \times 10^9$/L) and/or aged < 50 years. Altogether these cases represented 71% of CR patients. This finding differs from the German experience with the B-NHL 83/86 programs, in which all cases with $<50 \times 10^9$/L white blood cells (83% of evaluable cases) fared very well (DFS 71%), and probably means that the outcome of poor-risk patients, such as those reported herein, can be significantly improved by GMALL B-NHL regimens, whilst the advantage would probably be lost in low-risk patients.

Clearly, the type of chemotherapy was less influential during the postremission phase than in early treatment, with the possible exception of protocol 07/93 based on intermediate/high-dose short chemotherapy pulses plus unmanipulated CD34+ peripheral blood stem cell autograft. Five CR patients completed treatment, including autograft, and none relapsed. These data, in keeping with those of other studies,[25] suggest that peripheral blood contamination by B-ALL cells probably does not represent a major concern and emphasize the need of more patients and a longer follow-up in order to draw appropriate conclusions. In general, allogeneic marrow or peripheral blood stem cell transplants could be reserved for primarily refractory or recurrent cases, in agreement with Hoelzer *et al.*[1]

Recurrence analysis indicated a very short time to relapse, a high incidence of neuromeningeal progression, and no significant difference between adriamycin and idarubicin-treated patients. This last finding fits the general experience in adult ALL, where an intensive use of anthracyclines is not associated with an improved DFS in B/L_3-ALL.[20] The 19% incidence of CNS relapse with or without concomitant bone marrow involvement is higher than that reported in the GMALL series (6/45 CR patients or 13%) and was not reduced by the use of idarubicin (3/12 CR patients or 25% versus 1/9 or 11% with adriamycin regimens), indicating that idarubicinol offered no clinically effective protection despite its proven capacity of crossing the blood-brain barrier.[26] One explanation for the high CNS recurrence rate in our study might be the inappropriate delay in cranial radioprophylaxis, which was initiated after about 8-12 weeks of remission, since spread to CNS structures occurs very early in B-ALL. In GMALL studies B-NHL 83/86, irradiation to the skull (plus spinal cord in study 86) was delivered after the first two chemotherapy courses, that is a minimum of one month earlier, and the incidence of CNS disease was indeed lower (5/41 or 12%). However, the incidence of this complication appears to be higher than in other ALL subsets and more difficult to control, despite the concurrent administration of early radiation therapy, triple intrathecal therapy and systemic high-dose methotrexate, even in patients in whom sterilization of bone marrow disease is

otherwise achieved. Perhaps the concomitant evaluation of additional strategies, such as early high-dose ara-C or higher-dose methotrexate, might allow further therapeutic improvement.

In summary, our retrospective study showed that long-term DFS can be achieved in B/L$_3$-ALL and advaced-stage adult Burkitt's NHL with ALL-type regimens, especially in cases with <1×10^9/L absolute L$_3$ blast cells in the peripheral blood and/or age < 50 years. The use of idarubicin as the front-line anthracycline, improved chemo-radioprevention of CNS disease, and possibly the introduction of high-dose chemotherapy with autologous blood stem cell rescue are the lines along which these results should be further implemented.

References

1. Hoelzer D, Ludwig W-D, Thiel E, et al. Improved outcome in adult B-cell acute lymphoblastic leukemia. Blood 1996; 87: 495-508.

2. Fenaux P, Laj JL, Miaux O, Zandecki M, Louet JP, Bauters F. Burkitt cell acute leukaemia (L$_3$ ALL) in adults: a report of 18 cases. Br J Haematol 1989; 71:371-6.

3. Patte C, Michon J, Frappaz D, et al. Therapy of Burkitt and other B-cell acute lymphoblastic leukaemia and lymphoma: experience with the LMB protocol of the SFOP (French Paediatric Oncology Society) in children and adults. Baillière's Clin Haematol 1994; 7:339-48.

4. GIMEMA Cooperative Group. GIMEMA ALL 0183: a multicentric study on adult acute lymphoblastic leukaemia in Italy. Br J Haematol 1989; 71:377-86.

5. Ellison RR, Mick R, Cuttner J, et al. The effects of postinduction intensification treatment with cytarabine and daunorubicin in adult acute lymphocytic leukemia: a prospective randomized clinical trial by Cancer and Leukemia Group B. J Clin Oncol 1991; 9:2002-15.

6. Linker CA, Levitt LJ, O'Donnell M, Forman SJ, Ries CA. Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: a follow-up report. Blood 1991; 78:2814-22.

7. Fière D, Lepage E, Sebban C, et al. Adult acute lymphoblastic leukemia: a multicentric randomized trial testing bone marrow transplantation as postremission therapy. J Clin Oncol 1993; 11:1990-2001.

8. Bassan R, Battista R, Rohatiner AZR, et al. Treatment of adult acute lymphoblastic leukaemia (ALL) over a 16-year period. Leukemia 1992; 6 (Suppl 2):186-90.

9. Bassan R, Battista R, Montaldi A, et al. Reinforced HEAV'D therapy for adult acute lymphoblastic leukemia: improved results and revised prognostic criteria. Hematol Oncol 1993; 11:169-77.

10. Bassan R, Battista R, Viero P, et al. Intensive therapy for adult acute lymphoblastic leukemia: preliminary results of the idarubicin/vincristine/L-asparaginase/prednisolone regimen. Semin Oncol 1993; 20:(suppl. 8)39-46.

11. Bassan R, Battista R, Rossi G, et al. The use of intensive chemotherapy regimens in the treatment of adult acute lymphoblastic leukaemia. Paper presented at the satellite Symposium: Idarubicin in current treatment strategies for haematological malignancies. Harrogate (UK): 20th annual meeting of the European Group for Bone Marrow Transplantation, 1994: Extended Abstracts, 7.

12. Bassan R, Rambaldi A, Viero P, Borleri G, Barbui T. Integrated use of morphology, cytochemistry, and immune marker analysis to identify acute leukaemia subtypes. Haematologica 1989; 74:487-90.

13. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. Br J Haematol 1976; 33: 451-8.

14. Magrath IT, Jain V, Jaffe ES. Small noncleaved cell lymphoma. In: Knowles DM, ed. Neoplastic hematopathology, Baltimore:Williams & Wilkins, 1992:749-72.

15. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging. Cancer Res 1971; 31:1860-1.

16. Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphoma of childhood: an analysis of the histology, staging, and response to treatment in 338 cases in a single institution. J Clin Oncol 1989; 7:186-93.

17. Magrath IT, Janus C, Edwards BK, et al. An effective therapy for both undifferentiated (including Burkitt's) lymphoma and lymphoblastic lymphoma in children and young adults. Blood 1984; 63:1102-11.

18. Hoelzer D, Thiel E, Ludwig WD, et al. Follow-up of the first two successive German multicentre trials for adult ALL (01/81 and 02/84). Leukemia 1993; 7(Suppl 2):S130-4.

19. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL. Acute tumor lysis syndrome-a review of 37 patients with Burkitt's lymphoma. Am J Med 1980; 68:486-91.

20. Bassan R, Lerede T, Rambaldi A, Buelli M, Viero P, Barbui T. The use of anthracyclines in adult acute lymphoblastic leukemia. Haematologica 1995; 80:280-91.

21. Ross D, Tong Y, Cornblatt B. Idarubicin (IDA) is less vulnerable to transport-mediated multidrug resistance (MDR) than its metabolite idarubicinol (IDAol) or daunorubicin (DNR) (Abstract). Blood 1993; 82(Suppl 1):257a.

22. Goasguen JE, Dossot J-M, Bennett JM, Fauchet R. Multidrug resistance (MDR) associated P-170 glycoprotein is correlated to the cytology in ALL. Blood 1992; 80(Suppl 1):204a.

23. Ames MM, Spreafico F. Selected pharmacologic characteristics of idarubicin and idarubicinol. Leukemia 1992; 6(Suppl 1): 70-5.

24. Murphy SB, Bowman WP, Abromowitch M, et al. Results of treatment of advanced-stage Burkitt's lymphoma and B cell (SIg+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. J Clin Oncol 1986; 4:1732-9.

25. Sweetenham JW, Pearce R, Taghipour G, Goldstone AH. Adult Burkitt's and Burkitt-like non-Hodgkin's lymphoma (NHL)-Favourable outcome for patients undergoing high dose therapy and autologous stem cell transplantation (ASCT) in first remission or chemosensitive relapse: results from EBMT (Abstract). Blood 1995; 86(Suppl 1):211a.

26. Reid JM, Pendergrass TW, Krailo MD, et al. Plasma pharmacokinetics and cerebrospinal fluid concentrations of idarubicin and idarubicinol in pediatric leukemia patients. A Children's Cancer Study Group report. Cancer Res 1990; 50: 6526-8.