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Adult Acute Lymphoblastic Leukemia. Response to Therapy According to Presenting Features in 62 Patients

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Abstract—*Sixty-two adult patients with acute lymphoblastic leukemia (ALL) were treated with an induction regimen including vincristine, daunorubicin and prednisone (VDP) followed by CNS prophylaxis. Forty-five patients (72.5%) achieved complete remission (CR). The CR were maintained with daily 6-MP and weekly MTX. Monthly reinduction cycles with vincristine and prednisone (plus daunorubicin every three courses) were also given. Median duration of CR was* 10.4 months. *Overall survival was* 17.4 months. *The remission rate and length of CR were studied in relation to the clinical and hematological features present at diagnosis. CR rate was adversely influenced by age only over* 40 *and by tumoral presentation. The length of remission was negatively influenced by tumoral presentation, CNS involvement, high circulating blast count, L2 and L3 cytology, and T or B immunological phenotype. Multiple regression analysis confirmed the weight of FAB morphology in determining the length of remission. Among L2 adult patients, tumoral presentation appears to be the major unfavourable prognostic factor.*

INTRODUCTION

IT IS well-established that adult patients with acute lymphoblastic leukemia (ALL) have a worse prognosis than children. Significant improvements have been reported in recent studies on adult ALL by the addition of anthracycline antibiotics and new treatment modalities [1–4]. However, despite these encouraging results, the outlook for the disease in adults remains poor. In addition, broad differences of response and survival are observed not only between adult and childhood ALL but also within adult patients even treated with the same therapeutic protocol [1, 5]. This fact raises the necessity for detection of pretreatment prognostic factors useful in assigning patients to prognostic groups that may benefit from different therapeutic approaches.

The aims of this study are: (1) to report the results of the vincristine, daunorubicin, prednisone (VDP) induction program, followed by CNS prophylaxis and maintenance–reinduction treatment, in 62 cases of adult ALL and (2) to define the prognostic value of the pretreatment clinical and hematological features of the disease. This series of similarly treated patients may allow a reliable evaluation of prognostic factors since it rules out all the variables related to differences in treatment.

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MATERIALS AND METHODS

Patients

Sixty-two consecutive patients (42 men and 20 women), aged 12–59 yr (median age, 23 yr), with untreated ALL were treated with the same regimen at the Division of Hematology of Pavia between January 1974 and November 1980.

Cytologic diagnosis was made on the basis of May Grünwald-Giemsa stains and cytochemical stains for PAS, peroxidase, Sudan black, naphthol-ASD-acetate esterase (+/− inhibition by sodium fluoride) and acid phosphatase. Marrow smears were subclassified according to the FAB classification [6]. Moreover, the leukemias

were classified as T-ALL by spontaneous rosette formation with sheep erythrocytes, as B-ALL by the presence of monoclonal membrane immunoglobulins, as non-T, non-B-ALL if both tests were negative. In 21 patients blast cells were studied for the presence of terminal deoxynucleotidyl transferase (TdT) by biochemical [7] and immunofluorescence techniques. Cytogenetic analysis showed that all patients were Ph' negative.

The diagnosis of CNS leukemia was established on the basis of clinical signs and/or the presence of blast cells in cytocentrifuge preparations of the cerebrospinal fluid (CSF). Except in patients presenting with clinical signs of CNS involvement, lumbar puncture for CSF examination was performed only when complete hematological remission (CR) had been achieved. For each patient, the following pretreatment clinical features were also recorded: liver and spleen enlargement, presence of lymphadenopathy and mediastinal masses. A 'tumor group' was defined by the presence of liver or spleen enlargement 3 cm below the costal margin, and/or lymph nodes exceeding 3 cm in diameter, and/or mediastinal involvement.

Treatment program

Induction. All patients received the same induction therapy, consisting of vincristine 1.4 mg/m^2 plus daunorubicin 60 mg/m^2 intravenously once weekly, and prednisone 40 mg/m^2 orally daily. This treatment was given for 6 courses. In cases of cytopenia, the interval between the courses was increased and its length depended on the bone marrow findings.

CNS prophylaxis and treatment. Except in patients with clinical evidence of meningeal leukemia at presentation, CNS prophylaxis was started when hematological remission had been achieved. It consisted of cranial irradiation with a [^{60}Co] apparatus (2400 rads given in 12 fractions over three weeks), plus five doses of intrathecal methotrexate (12 mg/m^2 given twice weekly during radiotherapy). Patients with meningeal leukemia at presentation received the same treatment and 2 additional doses of intrathecal methotrexate.

Maintenance therapy. Patients who attained complete remission received 6-mercaptopurine (6-MP) 90 mg/m^2 orally daily and methotrexate (MTX) 15 mg/m^2 intravenously once weekly. The doses of both drugs were adjusted to maintain the white cell count at 3×10^9/l. Reinduction courses with a single dose of vincristine 1.4 mg/m^2 plus prednisone 40 mg/m^2/day for 7 days were repeated every month during the first year; a dose of daunorubicin 60 mg/m^2 was added to vincristine every three courses. After the first year of therapy the interval between reinduction courses was increased to three months. Maintenance therapy was continued for three years and then stopped.

Definition of response and statistical methods

Complete remission was defined as a state lasting for more than two months with: a normal peripheral blood count, a normocellular bone marrow with less than 5% blast cells and a normal CSF on cytocentrifuge preparations. Patients with CNS leukemia at hematological remission were considered to be in CR when blasts had been cleared from the CSF by CNS treatment. Bone marrow was examined routinely every three months; CSF was reexamined only in case of clinical indication. Relapse was defined as the reappearance of blast cells in the peripheral blood, bone marrow, or CSF. CR duration was calculated from the date of complete remission to relapse. Survival was the length of time from the date of diagnosis to death. The actuarial curves were calculated according to Berkson and Gage [8] and compared by the generalized Wilcoxon technique of Gehan [9]. The χ^2 test was used for comparing the effect of the pretreatment variables, grouped into convenient categories, on CR rate. The pretreatment characteristics affecting short and long-term prognosis are coded as follows: age (< 40 yr = 0; > 40 yr = 1), tumoral syndrome (absent = 0; present = 1), CNS involvement (absent = 0; present = 1), blast cell count ($< 35 \times 10^9$/l = 0; $> 35 \times 10^9$/l = 1), FAB subtypes (L1 = 0; L2 or L3 = 1) and surface markers (non-T, non-B-ALL = 0; T or B-ALL = 1). These categories were used to perform a multiple regression analysis in order to measure both the effect of the variables on the whole and the relative weight of the single variable in determining the variation on the length of complete remission.

RESULTS

Table 1 summarizes the pretreatment clinical and hematological features of the 62 patients who entered the study. All cases were treated with the same VDP protocol. The induction regimen was well-tolerated and no deaths occurred during the first six weeks of treatment. During CNS therapy a minority of patients complained of headaches and transient back and leg pain; except for alopecia, no late sequelae of the treatment have been observed.

Table 1. Frequency of main pretreatment clinical and hematological features in 62 adult patients with ALL

	Patients	
	No.	(%)
Age (years):		
range: 12–59 (median 23)		
< 40	52	(84)
> 40	10	(16)
Sex:		
males	42	(68)
females	20	(32)
Hepatomegaly (> 3 cm)	40	(64)
Splenomegaly (> 3 cm)	40	(64)
Lymphadenopathy	12	(19)
Mediastinal enlargement	6	(10)
CNS involvement	6	(10)
Blast count > 35×10^9/l	13	(21)
FAB category:		
L1	8	(13)
L2	51	(82)
L3	3	(5)
Surface markers:		
non-T, non-B-ALL	49	(79)
T-ALL	10	(16)
B-ALL	3	(5)

No patients had protocol violations during induction and the CNS phase.

Out of sixty-two patients, forty-five (72.5%) achieved complete clinical, hematological and CNS remission: 27 patients within 4 weeks, while 18 patients required 5–7 weeks of treatment. The remaining 17 patients who failed to respond to this induction protocol received other treatments and died 2–24 months after diagnosis. Three patients had clinical and cytological evidence of CNS leukemia at presentation, and three other asymptomatic patients showed blast cells in CSF at the time of hematological remission; blasts were cleared from CSF by CNS treatment in five of these cases. During maintenance therapy two patients developed pneumonia. Two other patients developed major liver function abnormalities, requiring MTX withdrawal. Individual dose adjustment of the drugs was often necessary.

The median CR duration of the 45 remitters was 10.4 months. Eight patients have been in first remission for 3.5–84 months; three of them have been off therapy for 16, 45, 48 months respectively. Thirty-seven patients relapsed within 3–78 months (one of them had been off therapy for 42 months). The site of first relapse was the bone marrow in 29 patients, the CNS in 6 and the testis in 2. Of the five patients with meningeal leukemia at presentation, two relapsed in the bone marrow (after 3 and 10 months) and two in the CNS and testis respectively (both at 8 months). A second complete remission was obtained in 4 patients (median duration 6 months).

The median survival for all patients was 17.4 months. Patients who achieved CR had a predicted median survival of 20.4 months, while non-remitters had a median survival of only 6.8 months (Fig. 1). The effect of pretreatment characteristics on remission rate and remission duration is shown in Table 2. Sex was correlated neither with the attainment of CR (males 73.8%; females 70%) nor with CR duration (males 10.6 months; females 8.6 months, $P = 0.25$).

The results of the multiple regression analysis are reported in Table 3. From the 45 remitters, 3 cases still in CR but with too short a follow-up have been excluded. For CR duration considered as the dependent variable, the square of the multiple correlation coefficient R^2 represents the proportion of variation explained by all the variables in the regression model. The relative weight of the single variable (measured as a percentage of the regression sum of squares) in determining the variation of the dependent variable is also shown.

In this study the number of TdT-tested cases is small (21 patients). Therefore, the further immunological classification of the non-T, non-B group into 'common' and 'null' ALL subtypes was not evaluated as a prognostic factor. However, 13 out of 15 non-T, non-B cases tested resulted TdT positive.

DISCUSSION

Response to the VDP protocol

The combination of vincristine, daunorubicin and prednisone (VDP), followed by cranial irradiation and intrathecal methotrexate, induced complete remission in 45 of 62 (72.5%) adult patients with ALL. Our results are comparable with the adult remission rates of about

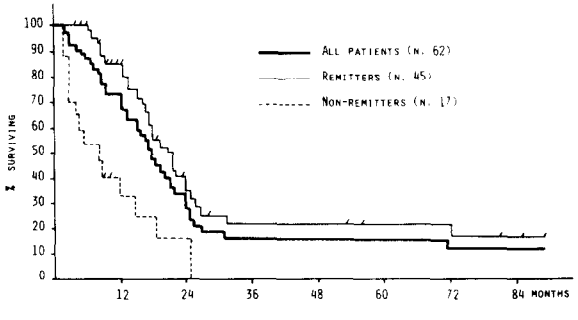

Fig. 1. Survival curves. Each patient surviving is represented by a dash.

Table 2. Clinical and hematological features at presentation affecting CR rate and CR duration

Pretreatment features	No. of patients	CR Rate			CR duration (months)			
		No.	%	P	Proportion in remission 75%	50%	25%	P
Total	62	45	72.5		6.5	10.4	13.6	
Age:								
>40	10	4	40	< 0.05	5.1	6.7	—*	NS
<40	52	41	78.8		6.3	10.5	13	
Tumoral syndrome:								
present	39	25	64.1	≃ 0.05	3.6	7.7	10.8	< 0.001
absent	23	20	86.9		9.1	12.8	36.9	
CNS involvement:								
present	6	5	83.3	NS	3.1	4.0	5.6	< 0.02
absent	56	40	71.4		6.7	10.9	17.2	
Blast cell count:								
$>35\times10^9$/l	13	8	61.5	NS	3.1	4.8	8.2	< 0.01
$<35\times10^9$/l	49	37	75.5		7.7	11.0	18.2	
FAB category:								
L_1	8	6	75	NS	11.9	37.7	80.7	< 0.001
L_2	51	38	74.5		6.3	9.5	12.7	
L_3	3	1	33.3			2.9		
Surface markers:								
non-T, non-B-ALL	49	38	77.5	NS	7.8	10.9	14.5	< 0.01
T-ALL	10	6	60		2.5	3.2	5.3	
B-ALL	3	1	33.3			2.9		

*Proportion not reached at 27.3 months.

Table 3. Results of multiple regression analysis on CR duration

Characteristic	Percentage of regression sum of squares	
FAB classification	62.62	
Tumoral presentation*	31.09	
Blast cell count	3.09	$R^2 = 40.03$
Surface markers	2.02	
CNS involvement	0.64	
Age	0.54	

*When only L2 and L3 cases are considered, 94.81% of the variation is explained by tumoral presentation.

75% obtained in previous studies by the addition of anthracyclines (+/− L-asparaginase) to the basic vincristine and prednisone regimen [1–4, 10, 11], but are inferior to the remission rates of over 90% currently achieved in children with similar induction therapies [3, 12].

The predicted median duration of CR (10.2 months) is comparable with the median duration of 8–14 months reported by several authors in adult ALL [10, 11, 13–15], but it is considerably lower if compared with the 18.5, 16.9 and 22 months obtained respectively by Lister *et al.* [2] with the OPAL scheme (vincristine, prednisolone, adriamycin and L-asparaginase), by Omura *et al.* [16] adding a 'consolidation' treatment early in remission, and by Ruggero *et al.* [4] with a vincristine–prednisone regimen and additional doses of daunorubicin and cyclophosphamide when required. The median CR duration was even longer (28 months) for adults with ALL treated by Gee *et al.* [1] with a very intensive early consolidation chemotherapy and a multidrug maintenance regimen (L2 protocol).

Our data confirm that the VDP combination can produce a high CR rate in adult ALL with minimal toxicity. However, despite these results, the median durations of remission and survival on conventional maintenance–reinduction regimens are short. These observations suggest that further improvements on remission duration could be obtained in the majority of adult ALL by more intensive multiple-drug consolidation and maintenance programs, whereas it appears reasonable to restrict the use of more aggressive induction modalities to patients with a poorer short-term prognosis.

Factors affecting the remission rate

The remission rate and length of remission were studied in relation to the clinical and biological characteristics present at diagnosis. Since the patients were all treated with the same VDP protocol, it seems reasonable to

assume that differences in disease outcome must reflect disease heterogeneity rather than differences in patient selection or management. Sex was not correlated with short-term prognosis. Patients over 40 yr showed a significantly lower remission rate independently of FAB classification, in agreement with the results of Ruggero *et al.* [4]. A tumoral presentation was also correlated with a poorer response to therapy. Nevertheless, peripheral blast cell count $> 35 \times 10^9/l$ was not found to exert any statistically significant influence on the achievement of CR, whereas in other larger studies [3] tumoral presentation and high blast cell count were correlated, and both negatively influenced the remission rate. L3 morphology adversely affected the response to therapy; no difference in remission rate was observed between L1 and L2 FAB subtypes. This is in agreement with Brearley *et al.* [17], but the small number of the L1 cases in our series prevents any definite assessment. Indeed, in other studies on adult ALL including higher percentages of L1 patients [13, 15], L2 morphology appeared to be correlated to a poorer immediate response compared to the L1 group. The few patients with B-cell leukemia had a worse response to therapy; the difference in remission rate between patients carrying T, or non-T, non-B immunological phenotypes was not statistically significant.

Our results with the VDP protocol confirm the prognostic importance on the remission rate of only a few of the pretreatment factors frequently cited as influencial; moreover, their level of significance is low. This fact is related to the effectiveness of the protocol employed. Therefore, it seems likely that pretreatment factors will be less influencial as short-term prognostic indicators when more effective induction modalities become available.

Factors related to long-term prognosis

Initial clinical and biological features appeared clearly linked to remission duration and survival, making it possible to group patients according to the expected long-term evolution of the disease. Sex was not related to the outcome; age over 40 yr only influenced survival ($P < 0.05$). The initial extent of disease, expressed by a tumoral presentation and a high circulating blast count, adversely influenced the length of CR. This finding is in agreement with several prior observations in adults [1, 2, 4, 13] and children [3, 18], but is different from those of Omura *et al.* [16] and Leimert *et al.* [15] on adult ALL. No significant correlation was observed in our study between tumor and blast cell count ($P > 0.05$), so that these two factors may independently affect adult ALL outcome. CNS leukemia at presentation was also of adverse prognostic significance on CR duration. Despite the small number of patients showing L1 cytology, our study shows a significantly better CR duration and survival for L1 than for L2 cases, independent of age. The weight of FAB morphology in determining the length of remission in adults is confirmed by the multiple regression analysis. These results agree with prior observations in childhood ALL [19, 20], but are different from other reports on children [21] and adults [13, 15, 17]. Burkitt-like (L3) leukemia is generally recognized as a poor prognosis disease.

The immunological classification, in terms of T, B or non-T, non-B surface characteristics, appeared to be a very important prognostic indicator. The proportion of these immunological types of leukemia in our series are similar to those reported by others [20, 22, 23]. All B-cell cases had L3 characteristics. All T-cell leukemias had L2 morphology owing to the small size of the L1 group; the significance of this association must be observed with caution. Indeed, in the previously cited series, the distribution of T and non-T, non-B-ALL within L1 or L2 types showed no differences. Here, the 10 cases of T-derived ALL showed a high male:female ratio (8:2); all patients were characterized by tumoral disease at presentation and six of them had a mediastinal mass, whereas no cases of non-T-ALL showed thymic enlargement; in four cases CNS leukemia was observed at onset or in relapse. Similar clinical features are described in children with T-ALL by Greaves *et al.* [21], but in contrast to these data, in our adult cases we failed to find the reported association with high white cell count. The same tumoral presentation was seen in the 3 cases of B-cell leukemia, all presenting with low circulating blast cell counts.

These observations confirm that expression of T or B phenotypes in adult ALL exerts a clearly negative influence on remission duration and survival when compared with non-T, non-B cases. T and B leukemias appear to be distinct clinical entities with tumoral presentation and a high risk of early relapse, probably reflecting specific biological features of these lymphoid lineages. This prognostic significance was also found in previous reports on children and adults [21, 23–25]. When only L2 and L3 cases are considered, the tumoral presentation appears to be the major prognostic factor in adult ALL, whereas WBC count is the most important prognostic indicator in children [21].

The adverse effect of T or B phenotype in adult ALL probably reflects its high correlation with the tumoral presentation ($P < 0.01$).

The pretreatment features analysed in this study also maintain their prognostic value if we restrict the analysis to the non-T, non-B-cell group.

In conclusion, our results indicate that many of the clinical and biological factors recognized to be of prognostic importance in childhood ALL also influence the outcome in adult ALL. Nevertheless, while only 20% of newly diagnosed childhood ALL present with initial poor prognosis features, a much higher proportion of adult cases carry one or more 'high risk' factors at presentation. This different proportion between 'high risk' and 'standard risk' cases account for the striking differences in outcome between childhood and adult ALL. Moreover, the variability in proportion between cases at different risk might explain the discrepancies in therapeutic achievement among some adult series.

From our and from other currently available data [3, 5], it appears necessary for therapeutic purposes to stratify not only children but also adult ALL patients into different risk groups according to simple and well-defined prognostic factors present at diagnosis. The recognition of prognostic groups may allow an objective evaluation and comparison of different regimens, and will aid in designing new therapeutic strategies.

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