# Prognostic Factors in a Multicenter Study for Treatment of Acute Lymphoblastic Leukemia in Adults

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**In a prospective multicenter study, 368 acute lymphoblastic leukemia (ALL) patients aged 15 to 65 years were treated with an intensified induction and reinduction regimen; 272 (73.9%) achieved complete remission (CR). The median remission duration (MRD) is 24.3 months, and the probability of being in continuous CR (CCR) at >5 years is .37. The median survival for all 368 patients is 27.5 months, and the probability of being alive at 5 years is .39. For the 272 patients in remission the median survival is 58.4 months, and the probability of being alive at 5 years is .49. A lower CR rate was seen for patients with bleeding at diagnosis or with splenomegaly/hepatosplenomegaly. The prognostic factors unfavorable for remission duration were time to CR >4 weeks *v* <4 weeks (*P* = .0002), age >35 years *v* <35 years (*P* = .0008), leukocyte count >30,000/μL *v* <30,000/μL (*P* = .0112), and null ALL *v* common ALL (c-ALL)/T cell ALL (T-ALL) (*P* = .05). The remission duration correlated strongly (*P* = .0001) with the number of these independent prognostic factors. In patients with none of these adverse factors the MRD has not yet been reached, with one adverse factor the MRD is 21.9 months, and with two or three adverse factors the MRD is only 9.6 months. For the immunologic subtype T-ALL, the probability of being in CCR at >5 years is .55; for c-ALL, .34; and for null ALL, .24. According to these results, patients were stratified into a low-risk group with a CCR rate of .62 and a high-risk group with a CCR rate of .28, with the latter now allocated to either further chemotherapy or bone marrow transplantation in first remission.**


TREATMENT RESULTS in adult acute lymphoblastic leukemia (ALL) have considerably improved with modern treatment modalities, with disease-free survival rates of 20% to 45% at 3 years or thereafter,[1-9] and a substantial proportion of these patients may be cured. Also, bone marrow transplantation in younger adults with ALL in first or second complete remission (CR) shows very promising results with similar or even better continuous CR (CCR) rates.[10-16] Thus the definition of parameters that are predictive for the length of disease-free survival becomes important to select poor-risk patients who should receive transplants in first remission or receive further chemotherapy.

The effect of intensified induction and consolidation therapy was evaluated in 162 patients of the German prospective multicenter study for treatment of adult ALL.[2] The present report gives the follow-up of that multicenter study for 368 patients. One of the main objectives was to find factors that were prognostic for the achievement of CR and for the duration of remission. Special attention was given to an evaluation of the influence of single prognostic factors. This was made possible by the large number of patients who were treated with the same protocol and had uniform central morphological, cytochemical, and immunologic diagnoses.

## MATERIALS AND METHODS

### *Patient Recruitment*

From October 1978 to June 1983 a total of 384 patients from 33 hospitals entered the study. According to the entry criteria, patients between the ages of 15 and 65 years with the morphological and cytochemically confirmed diagnosis of ALL or acute undifferentiated leukemia (AUL) who were without prior malignancy, severe prior illness, or psychiatric disease were eligible. All patients were registered for the study before receiving chemotherapy. From these 384 patients, 16 had to be excluded for various reasons: refusal of therapy and social reasons (two), violation of the induction therapy protocol (four), or inadequate data (ten), which left 368 patients for the final analysis (Table 2). The evaluation date was November 30, 1986. All patients were advised of the procedures and attendant risks involved in the therapy and gave their written consent to enter the study.

### *Diagnostic Procedure*

After diagnosis at the recruiting hospital, pretreatment bone marrow and peripheral blood slides were sent for central morphological and cytochemical classification (H. Löffler, Kiel) and bone marrow and peripheral blood samples for central immunologic phenotyping (E. Thiel, Munich). Karyotype analysis was not carried out systematically in this study with 33 participating hospitals, but the few patients known to be Philadelphia chromosome–positive were not excluded from the statistical analysis.

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**Table 1. Treatment Schedule for Adult ALL**

| Drug | Dose | Days |
|---|---|---|
| Induction | | |
| Phase 1 | | |
| Prednisone (PO) | 60 mg/m$^2$ | 1-28 |
| Vincristine (IV)* | 1.5 mg/m$^2$ | 1, 8, 15, 22 |
| Daunorubicin (IV) | 25 mg/m$^2$ | 1, 8, 15, 22 |
| L-asparaginase (IV) | 5000 U/m$^2$ | 1-14 |
| Phase 2 | | |
| Cyclophosphamide (IV)† | 650 mg/m$^2$ | 29, 43, 57 |
| Cytosine arabinoside (IV) | 75 mg/m$^2$ | 31-34, 38-41, 45-48, 52-55 |
| 6-mercaptopurine (PO) | 60 mg/m$^2$ | 29-57 |
| Methotrexate (IT)‡ | 10 mg/m$^2$ | 31, 38, 45, 52 |
| Reinduction | | |
| Phase 1 | | |
| Dexamethasone (PO) | 10 mg/m$^2$ | 1-28 |
| Vincristine (IV) | 1.5 mg/m$^2$ | 1, 8, 15, 22 |
| Adriamycin (IV) | 25 mg/m$^2$ | 1, 8, 15, 22 |
| Phase 2 | | |
| Cyclophosphamide (IV)† | 650 mg/m$^2$ | 29 |
| Cytosine arabinoside (IV) | 75 mg/m$^2$ | 31-34, 38-41 |
| Thioguanine (PO) | 60 mg/m$^2$ | 29-42 |
| Maintenance | | |
| 6-mercaptopurine (PO) | 60 mg/m$^2$ | daily } weeks 10-18 |
| Methotrexate (PO/IV) | 20 mg/m$^2$ | weekly } and 29-130 |

*Maximum single dose, 2 mg.
†Maximum single dose, 1,000 mg.
‡Maximum single dose, 15 mg.

*Morphology.* The morphological diagnosis was based on May-Grünwald-Giemsa and cytochemical staining of bone marrow and blood smears, including PAS, peroxidase, naphthylacetate esterase, and facultatively, acid phosphatase. Classification criteria have been described previously.[2,17]

*Immunology.* Between October 1978 and June 1983 heparinized blood and bone marrow samples from 248 of the total 368 patients (67%) were received in the central laboratory for immunologic marker analysis.

Blast cells for phenotype determination were isolated by standard Ficoll-Isopaque density gradient centrifugation. Rosette assays with untreated and S-(2-amino-ethyl): sothiouronium bromide hydrobromide (AET)–treated sheep erythrocytes and 7s-coated ox erythrocytes were performed; immunofluorescence stainings with polyclonal anti-T, anti-c-ALL antigen (CALLA), antimyeloid and anti-Ig antisera were performed as already described.[18] The binding of murine antibodies (MoAbs) and an ascites control was assessed with fluorchrome-labeled, affinity-purified IgGF(ab)$_2$ fragments of goat antimouse Ig by indirect immunofluorescence methods.[19]

Starting in 1980, the following MoAbs according to World Health Organization nomenclature[20] were used, with mixtures of MoAbs against major antigens being composed to avoid false-negative results due to lack of a given epitope: VIL-A1 (CD10) against CALLA (kindly provided by W. Knapp), OKT1 against Ia (HLA-DR) antigens, OKT6 and NA134 against cortical thymocyte antigen HTA-1 (CD1), Lyt3 and OKT11 against E receptor–associated antigen (CD2), UCHT1 (kindly provided by P. Beverly) and OKT3 against mature T cell receptor–associated antigen (CD3), Leu1 and Lyt2 against a pan-T and B subset/chronic lymphocytic leukemia (CLL) antigen (CD5), WT1 (kindly provided by W. Tax) against a pan-T antigen (CD7), BA-1 against a pan-B and mature granulocyte antigen (CD24), B1 against a B/pre-B antigen (CD20), 63D3 and VIM13 against monocytic antigens, and VIM D5 and VIM2 (kindly provided by W. Knapp) against myeloid antigens MyA. At least 200 cells were examined under an epiillumination microscope, and the criterion for positivity was expression of the marker by at least 20% of the blast cell population.

Comparisons of MoAbs with polyclonal anti-T and anti-CALLA antisera in phenotyping of frozen cell samples revealed a 95% concordance of VIL-A1 and rabbit anti-CALLA, whereas several MoAbs against T cells (CD1, CD2, CD3, CD5) were needed to substitute T cell–specific absorbed rabbit antithymocyte sera.[19] The WT1 MoAb (CD7), however, turned out to be a complete substitute for rabbit anti-T but was introduced at a later occasion (after 1983). Because many of the blood and bone marrow samples have been kept frozen and thus could be retyped by MoAbs, only 42 of the 248 cases have been phenotyped without MoAbs. The following subclassification of ALL was used: (*a*) common ALL (CALLA+, BA-1+, T−, E−, surface Ig–negative [sIg−]); (*b*) T-ALL (CALLA− or CALLA weakly positive, BA-1+, T+, E+, sIg−); (*c*) pre–T-ALL (CALLA−, BA-1+, T+, E−, sIg−); (*d*) B-ALL (CALLA− or

**Table 2. Results of the Adult ALL/AUL Study**

| | |
|---|---|
| Patients recruited | 384 |
| Evaluable | 368 |
| Recruiting centers | 33 |
| Complete remission | 272 (73.9%) |
| Failures | 96 |
| Partial remission | 17 (4.6%) |
| Aplasia | 6 (1.6%) |
| Death during induction | 41 (11.1%) |
| Non-responders | 32 (8.7%) |
| Deceased in CR | 8 |
| BMT in first CR | 3 |
| Relapse | 156 |
| Continuous CR | 105 |

CALLA+, BA-1+, T−, E−, sIg+); (*e*) null-ALL (CALLA−, Ia+, BA-1+/−, MyA+/−, T−, E−, sIg−).

### *Treatment Protocol*

The drugs and doses used in the induction and consolidation regimens are listed in Table 1. Induction therapy was given over an 8-week period with prednisone, vincristine, daunorubicin, and L-asparaginase during the first 4 weeks and cyclophosphamide, cytosine arabinoside, and 6-mercaptopurine during the second 4 weeks. As reinduction therapy, dexamethasone, vincristine, and doxorubicin were given for 4 weeks followed by cyclophosphamide, cytosine arabinoside, and thioguanine for 2 weeks. CNS prophylaxis consisted of cranial irradiation with 24 Gy and intrathecal methotrexate, 10 mg/m$^2$ (maximum single dose, 15 mg), once weekly for four weeks during phase II when CR was achieved after phase I. If remission was delayed until after completion of phase II, CNS prophylaxis was given immediately thereafter. Treatment of CNS disease, dose modification for patients older than 35 years, supporting therapy, and criteria for response have been described earlier.[2]

### *Statistical Methods*

The statistical evaluation was carried out by the Biometric Centre for Therapy studies (D. Messerer, Munich). To extract prognostic factors, the patients were stratified according to 30 different entrance parameters and two course parameters. The influence of these characteristics on the achievement of CR was evaluated by $\chi^2$ tests. The remission duration for each stratum was estimated by the Kaplan-Meier method,[21] and the strata were compared by univariate Mantel-Cox tests.[22,23] Multicollinearities, ie, correlations between prognostic factors, were tested by multivariate analysis. To identify factors of independent value, the initial characteristics were analyzed simultaneously with Cox's proportional hazards model.[23] For this analysis, surface marker phenotypes were classified in two versions: c-ALL and T-ALL in one stratum *v* null-ALL as well as each of these phenotypes separately.

## RESULTS

### *Pretreatment Characteristics*

The frequencies of the main entrance parameters in the 368 patients including clinical manifestations, laboratory parameters, immunologic diagnosis, and course parameters are given in Table 3. Compared with the first 162 patients in the study the distribution is very similar, with a predominance of younger patients (median age, 25 years) and male sex. An elevated WBC count over 30,000/$\mu$L was found in 36.1% and over 100,000/$\mu$L in 16.9%. A mediastinal mass, in most but not all instances of T-ALL, was observed in 12.5% of patients. CNS disease, confirmed by spinal cytology, was found in 6.5%. The frequency of immunologic subtypes in the 248 typed patients was common-ALL (c-ALL) in 115 (46.4%), T-ALL in 44 (17.7%), pre–T-ALL in 6 (2.4%), null ALL in 58 (23.4%), B-ALL in 4 (1.6%), mixed ALL in 4 (1.6%), and 17 (6.9%) could not be classified with certainty.

### *Remission Induction*

Results of induction therapy are given in Table 2. In 73.9% of the 368 patients a CR was obtained. This was achieved within 4 weeks in 59.8%, and 14.1% needed phase II of induction therapy before CR was reached. Seventeen (4.6%) of the patients had a partial remission, 1.6% had a persistent aplasia, 8.7% were nonresponders, and death during the induction period from day 1 to day 56 occurred in 11.1%.

Eight patients died in CR, three after induction therapy, three during reinduction therapy, and two during maintenance therapy. The cause of death was severe infection in seven patients (septicemia in four, pulmonary infection in three) and apoplexy in one. Three patients had bone marrow transplantation in first remission. These 11 patients are censored for remission duration.

A significantly lower CR rate was observed (Table 3) for patients with bleeding at diagnosis ($P$ = .009), splenomegaly ($P$ = .008), and hepatosplenomegaly ($P$ = .004). Patients with CNS involvement had a low CR rate of only 58.3%, but the difference from that for patients without CNS involvement was not significant. The 50 patients with T-ALL had a higher response rate of 82% compared with those with c-ALL (71.3%) or null ALL (67.2%). Out of the four patients with B-ALL only one achieved CR, and within the group of mixed leukemia two of four patients reached CR.

The frequency and nature of the side effects experienced were very similar to those in the first 162 patients reported.[2]

### *Survival Time*

The survival curves for the total 368 patients and for the 272 complete responders are shown in Fig 1. The median survival time for all 368 patients is 27.5 months, and the probability of survival at 5 years is .39 ± .06 CI (confidence interval). For the 272 remitters, the median survival time is 58.4 months, and the probability of being alive at 5 years is .49 ± .07 (CI). The median survival time for the 55 patients who achieved only partial remission or who did not respond is 7.6 months.

### *Remission Duration and Prognostic Factors*

The median remission duration (MRD) for the 272 patients (Fig 1) is 24.3 months, and the probability of being in CR at 5 years is .37 ± .07 (CI). The latest relapse occurred at 64 months.

Of the variables tested for their influence on remission duration, four were found to be statistically significant ($P$ < .05), namely, the time needed to achieve CR, age, initial leukocyte count, and the immunologic subtype. The correlation between remission duration and age was analyzed in 10-year steps from ages 15 to 65 years, and the cutoff giving the most significant difference was found to be 35 years. Similarly, the influence on remission duration of the initial leukocyte count was analyzed in steps of 10,000/$\mu$L, and the most significant cutoff was 30,000/$\mu$L. Late achievement of CR (Table 3) was the most significant adverse prognostic factor ($P$ = .0002), with an MRD of only 9.7 months compared with 31.4 months for those patients who achieved CR within 4 weeks. Age below or above 35 years was the next most significant factor ($P$ = .0008) with an MRD of 31.4 in younger patients compared with 15.4 months for the 35- to 65-year-old group. In patients with an initial leukocyte count below 30,000/$\mu$L, the MRD was 32.3 months compared with 15.2 months in those with >30,000/$\mu$L ($P$ = .0112). Multi-

**Table 3. Entrance and Response Parameters in Relation to Complete Remission Rate and Remission Duration**

| | | CR rate | | Remission Duration | | |
|---|---|---|---|---|---|---|
| | Frequency (%) | % | P | Median (mo) | Probability of CCR at 5 Years ± CI | P |
| Total | 368 | 73.9 | | 24.3 | 0.37 ± 0.07 | |
| Age | | | | | | |
| <35 yr | 271 (73.6) | 76.8 | | 31.4 | 0.43 ± 0.07 | .0008 |
| >35 yr | 97 (26.4) | 66.0 | | 15.4 | 0.21 ± 0.12 | |
| Sex | | | | | | |
| male | 221 (60.1) | 74.2 | | 21.8 | 0.36 ± 0.08 | |
| female | 147 (39.9) | 73.5 | | 31.7 | 0.41 ± 0.11 | |
| Bleeding* | | | | | | |
| – | 236 (64.1) | 78.4 | 0.009 | 25.2 | 0.37 ± 0.08 | |
| + | 132 (35.9) | 65.9 | | 17.4 | 0.41 ± 0.11 | |
| Infection* | | | | | | |
| – | 212 (57.6) | 75.9 | | 20.0 | 0.37 ± 0.08 | |
| + | 156 (42.4) | 71.2 | | 32.0 | 0.40 ± 0.11 | |
| Lymphadenopathy | | | | | | |
| – | 142 (38.6) | 72.5 | | 23.8 | 0.37 ± 0.10 | |
| + | 226 (61.4) | 74.8 | | 23.9 | 0.39 ± 0.08 | |
| Mediastinal mass | | | | | | |
| – | 322 (87.5) | 73.6 | | 23.1 | 0.35 ± 0.07 | |
| + | 46 (12.5) | 76.1 | | mnr | 0.56 ± 0.17 | |
| Hepatomegaly | | | | | | |
| – | 184 (50.0) | 78.8 | | 30.3 | 0.43 ± 0.09 | |
| + | 184 (50.0) | 69.0 | | 20.5 | 0.34 ± 0.09 | |
| Splenomegaly | | | | | | |
| – | 162 (44.0) | 80.9 | 0.008 | 26.6 | 0.39 ± 0.09 | |
| + | 206 (56.0) | 68.4 | | 21.6 | 0.38 ± 0.09 | |
| Hepatosplenomegaly | | | | | | |
| – | 229 (62.2) | 79.0 | 0.004 | 28.2 | 0.42 ± 0.08 | |
| + | 139 (37.8) | 65.5 | | 19.8 | 0.31 ± 0.11 | |
| CNS involvement | | | | | | |
| – | 342 (92.9) | 75.1 | | 23.9 | 0.38 ± 0.07 | |
| + | 24 (6.5) | 58.3 | | mnr | 0.51 ± 0.29 | |
| Leukocyte count | | | | | | |
| <30,000/μL | 235 (63.9) | 75.7 | | 32.3 | 0.42 ± 0.08 | .0112 |
| >30,000/μL | 133 (36.1) | 70.7 | | 15.2 | 0.32 ± 0.10 | |
| Granulocyte count | | | | | | |
| <500/μL | 81 (23.2) | 81.5 | | 31.8 | 0.37 ± 0.13 | |
| >500/μL | 268 (76.8) | 72.4 | | 23.0 | 0.38 ± 0.07 | |
| Platelet count | | | | | | |
| <25,000/μL | 120 (32.7) | 69.2 | | 17.5 | 0.41 ± 0.11 | |
| >25,000/μL | 247 (67.3) | 76.1 | | 25.2 | 0.38 ± 0.08 | |
| Immunology | | | | | | |
| c-ALL | 115 (51.6) | 71.3 | | 16.4 | 0.34 ± 0.11 | |
| T-ALL | 50 (22.4) | 82.0 | | mnr | 0.55 ± 0.17 | .0141 |
| null-ALL | 58 (26.0) | 67.2 | | 15.2 | 0.24 ± 0.15 | |
| Pre-phase therapy | | | | | | |
| – | 229 (62.2) | 75.1 | | 23.0 | 0.38 ± 0.08 | |
| + | 139 (37.8) | 71.9 | | 26.1 | 0.39 ± 0.11 | |
| Time to CR | | | | | | |
| <4 weeks | 220 | | | 31.4 | 0.42 ± 0.07 | .0002 |
| >4 weeks | 52 | | | 9.7 | 0.23 ± 0.13 | |
| Low-risk group | 44 | | | mnr | 0.62 ± 0.16 | .0004 |
| High-risk group | 118 | | | 15.5 | 0.28 ± 0.09 | |

Abbreviation: mnr, median not reached.

*WHO grade 2-4.

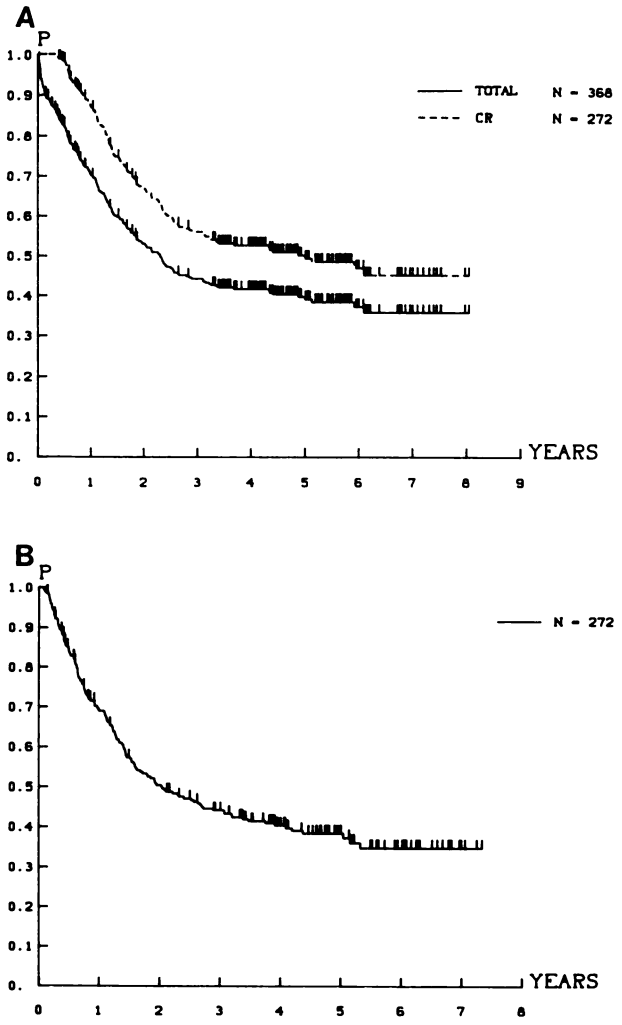


**Fig 1. (A) Probability of survival estimated by the Kaplan-Meier method for all evaluable patients and for patients with CR. (B) Probability of CCR estimated by the Kaplan-Meier method.**

variate analysis showed that these four factors were independent of each other.

The CR rate of all 248 phenotyped patients was 73.4%, the MRD was 22.3 months, and the probability of being in CCR at 5 years was .37 ± .07 (CI), which indicates that the phenotyped patients are representative of the whole group. For further analysis of the influence of immunologic subtype on remission duration, only the 162 CR patients composing the larger subtype groups c-ALL, T-ALL, or null ALL were considered, thus omitting the other phenotyped remitters (one of four patients with B-ALL, two of four mixed ALL, and 17 CR patients with uncertain phenotype).

Figure 2 gives the remission duration for the subtypes T-ALL, c-ALL, and null ALL. For the 41 remitters with T-ALL the MRD has not yet been reached, and the probability of being in CCR is .55 ± .17 (CI). For null ALL, the MRD is only 15.2 months, and the probability of being in CCR is .24 ± .17 (CI). The patients with c-ALL had an

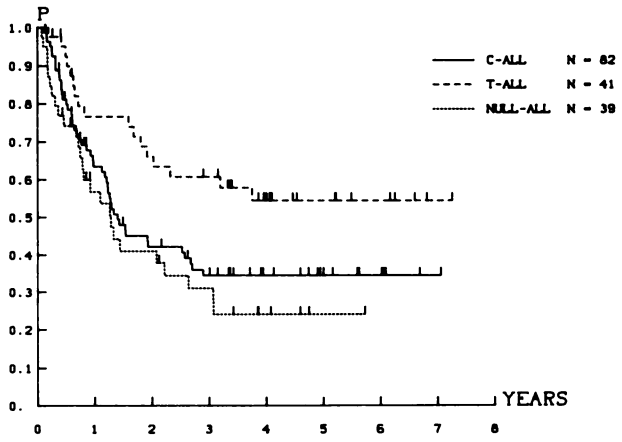


**Fig 2. Probability of CCR for patients having the immunologic subtype c-ALL, T-ALL, or null ALL. This analysis includes all patients of each subtype, with or without adverse factors.**

intermediate outcome, with an MRD of 16.4 months and a probability of CCR of .34 ± .11 (CI).

The length of disease-free survival was clearly dependent ($P$ = .0001) on whether a patient had 0, 1, 2, or 3 of the adverse factors: late achievement of CR, age >35 years, leukocyte count >30,000/$\mu$L, or null ALL (Fig 3). For patients without any of these factors the MRD has not been reached. For the patients with any one of the factors the MRD is 21.9 months, for those with two it is 12.0 months, and for those with three factors it is 5.2 months. Correspondingly, the CCR rate decreased from .62 for patients with no adverse factors to .11 for patients with three factors (Table 4). The differences in remission duration are significant, with $P$ = .0061 for none $v$ one factor, $P$ = .0207 for one $v$ two or three factors, and $P$ = .0474 for two $v$ three factors.

The frequency distribution of adverse prognostic factors is given in Table 4. Forty-four of the 162 typed patients with CR (27.7%) had no adverse factors, the majority (46.9%) had only one, 20.4% had two, 5.5% had three, and none had four. The most frequent adverse prognostic factor in all these groups was a high initial leukocyte count (Table 4).

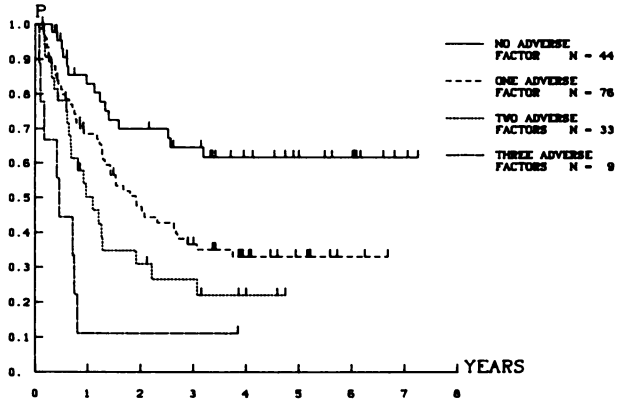


**Fig 3. Probability of CCR for patients having 0, 1, 2, or 3 adverse prognostic factors.**

**Table 4. Frequency of Adverse Factors in Relation to Remission in Adult ALL**

| | n (N = 162) | Remission Duration: Median (mo) | Remission Duration: Probability of CCR at 5 yr ± CI | |
|---|---|---|---|---|
| None | 44 (27.2%) | mnr | 0.62 ± 0.16 | P = .0061 |
| One factor | 76 (46.9%) | 21.9 | 0.33 ± 0.12 | |
| Leukocytes > 30,000/μl | 34 | 20.9 | 0.34 ± 0.18 | |
| Age > 35 years | 17 | 22.8 | 0.27 ± 0.23 | P < .0207 |
| Null-ALL | 14 | 23.5 | 0.29 ± 0.28 | |
| CR after > 4 weeks | 11 | 3.4 | 0.45 ± 0.30 | |
| Two factors | 33 (20.4%) | 12.0 | 0.22 ± 0.16* | P = .0474 |
| Three factors | 9 (5.5%) | 5.2 | 0.11 ± 0.21† | |
| Four factors | 0 | | | |

*At 4½ years.

†At 3½ years.

The group of 76 patients (Table 4) having only one adverse prognostic factor permitted an analysis of the separate influence of each factor. Figure 4 gives the remission duration curves for patients with either an initial leukocyte count above 30,000/μL, age above 35 years, or CR after more than 4 weeks, each without other adverse prognostic factors. Although the relapse pattern for patients with only a high leukocyte count or age above 35 years are quite similar, the relapse pattern for the small group of patients with late CR as their only adverse factor was markedly different, with a high initial relapse rate resulting in an MRD of only 3.4 months followed by a plateau phase.

Multivariate analysis was used to test whether any combination of two adverse factors was more predictive than others for remission duration. Of the 33 patients with two adverse factors, those ten patients with the combination of high leukocyte count and older age seemed the most unfavorable with an MRD of 8.9 months and a probability of CCR at 5 years of .19 ± .32 (CI); however, the difference was not significant owing to the small sample size.

Figure 5 illustrates the outcome for those patients with T-ALL, c-ALL, or null ALL without the adverse factors late CR, leukocyte count >30,000/μL, or age >35 years. For patients with c-ALL or T-ALL the probabilities of CCR, .57 and .73, are clearly much better than those for the total groups (Fig 2), whereas for patients with null ALL the outcome is only slightly worsened when other adverse factors are present.

To illustrate further the influence of adverse factors on a given immunologic subtype, Table 5 contrasts the MRD and probability of CCR at 5 years for c-ALL, T-ALL, and null ALL with or without adverse prognostic factors. The difference is significant only for the subtype c-ALL ($P$ = .0015). Similarly, when patients with each adverse factor alone are compared with those having additional adverse factors, only a high leukocyte count is significantly worsened ($P$ = .0221) by other adverse factors.

The analysis of prognostic factors in this study allowed us to stratify patients (Fig 6) into a low-risk group having no adverse prognostic factors and a high-risk group having one or more of the adverse prognostic factors. For the 118 high-risk patients, the MRD is 15.5 months, and the probability of CCR is .28 ± .09 (CI), whereas for the 44 low-risk patients the MRD has not yet been reached, and the probability of CCR is .62 ± .16 (CI).

*Relapse Distribution*

Up to the last evaluation date, November 30, 1986, 156 of the 272 remitters had relapsed. The major relapse site was

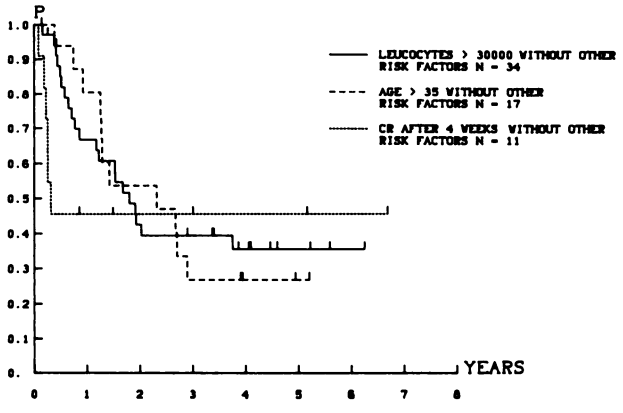


**Fig 4. Probability of CCR for patients having only a single adverse prognostic factor, either elevated leukocyte count, older age, or late CR.**

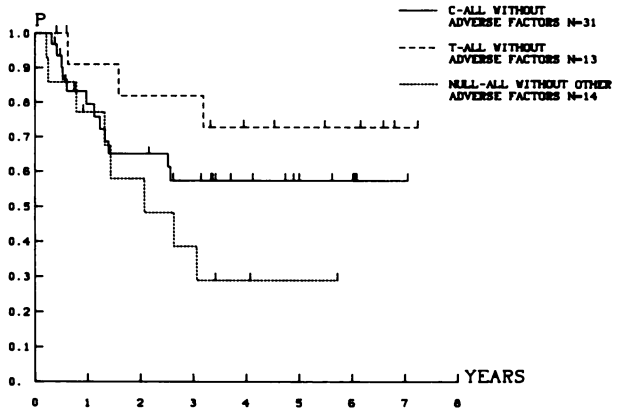


**Fig 5. Probability of CCR for patients having varying immunologic subtypes without other adverse factors, ie, patients with leukocyte counts <30,000/μL, and age <35 years, and CR after phase I.**

**Table 5. Remission Duration in the Immunologic Subtypes and in Patients Having Only High Leukocyte Count or Higher Age or Late CR**

| | Adverse Factors | N | Remission Duration: Median (mo) | Remission Duration: Probability of CCR at 5 yr ± CI | P |
|---|---|---|---|---|---|
| c-ALL | − | 31 | mnr | 0.57 ± 0.19 | .0015 |
| | + | 51 | 14.1 | 0.20 ± 0.12 | |
| T-ALL | − | 13 | mnr | 0.73 ± 0.27 | .1440 |
| | + | 28 | 34.1 | 0.47 ± 0.20 | |
| null-ALL | − | 14 | 23.5 | 0.29 ± 0.28 | .2277 |
| | + | 25 | 9.9 | 0.22 ± 0.18 | |
| WBC > 30,000/μL | − | 34 | 20.9 | 0.34 ± 0.17 | .0221 |
| | + | 30 | 8.9 | 0.16 ± 0.15 | |
| Age > 35 yr | − | 17 | 22.8 | 0.27 ± 0.22 | .0945 |
| | + | 21 | 8.5 | 0.21 ± 0.21 | |
| CR > 4 wk | − | 11 | 3.4 | 0.45 ± 0.30 | .3951 |
| | + | 17 | 7.2 | 0.18 ± 0.18 | |

bone marrow in 125 patients (80%). CNS as primary relapse site was observed in 17 patients (11%), and in four patients (3%) there was a simultaneous relapse in bone marrow and CNS. Five patients had the following sites as primary relapse: testes in two, lymph nodes in one, lymph nodes and ovary in one, and pleura and cutis in one. In the remaining five patients it was not possible to determine with certainty the primary site of relapse. It might be assumed that the pattern of relapse differs with various prognostic factors, eg, the immunologic subtype. However, no statistically significant correlation was found.

## DISCUSSION

The results of intensive treatment in adults with ALL/AUL found in the first 162 patients[2] have now been confirmed in a total of 368 patients. The CR rate, as also the remission duration and survival, rank among the most favorable for adult ALL when large multicenter trials are considered.[15,24-26] The fact that 33 hospitals participated in the study and that over half of them recruited on the average only one to two patients per year indicate that the therapy protocol is practical and reproducible.

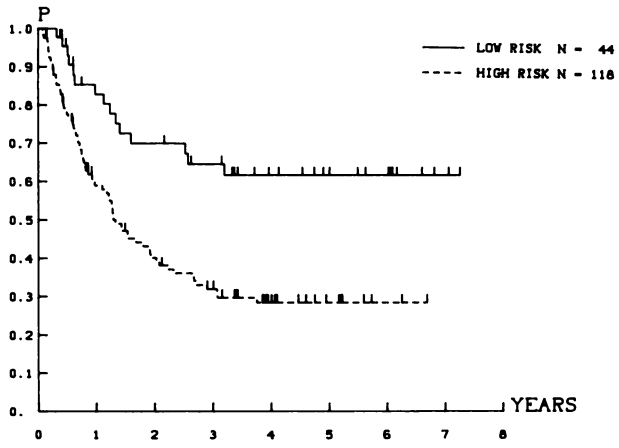


**Fig 6. Probability of CCR for patients with no adverse prognostic factors (low risk) and for patients with one or more of the adverse factors CR after >4 weeks, age >35 years, and initial leukocyte count >30,000/μL (high risk).**

A variety of entrance parameters that could influence the achievement of CR in adult ALL have been reported, such as morphology according to French-American-British criteria,[8,9,25,27,28] immunologic subtype,[25,29] karyotype,[28,30,31] sex,[32,33] age,[3,4,7-9,33-35] or initial leukocyte count.[8,29,36] In our study only patients with the initial symptoms of bleeding or splenomegaly/hepatosplenomegaly had a significantly lower CR rate (Table 3). There was a correlation between these two factors that might be explained by sequestration of platelets in the enlarged organs. Bleeding was also the major or a contributory cause of death because 14 of 26 patients who died during the first 4 weeks had a fatal hemorrhage. Involvement of the CNS at diagnosis resulted in a lower CR rate, as in other studies,[4,36] although the difference in our study was not statistically significant, probably owing to the large difference in sample size.

Consistent with the first 12 T-ALL patients treated according to this protocol,[2] the group of 50 patients with T-ALL had the highest CR rate with 82%. In other recent adult ALL trials high CR rates of 83% to 100%[25,33,37-39] have also been observed for this subtype. The general improvement for adult patients with T-ALL is remarkable in view of the fact that, as in childhood T-ALL, there is male predominance and a high proportion of patients with mediastinal mass, CNS involvement, or a high WBC count.

As in our previous study,[2] time to achieve CR, age, WBC count, and immunologic subtype had a significant influence on remission duration. With the larger number of 272 remitters, no other prognostic factors emerged, and these four are still found to be independent by multivariate analysis. Bleeding and splenomegaly/hepatosplenomegaly, predictive for achievement of CR, had no impact on remission duration. Late achievement of CR, the strongest adverse prognostic factor in our study, has also been found to have an adverse influence on disease-free survival in another ALL study.[25] Several adult ALL trials demonstrate that increased age is associated with shorter remission duration and decreased survival. However, differences in remission duration are often only evident when extreme age groups are compared.[3,25,40] In our study, patients between 35 and 65 years old had a poor outcome, with a probability of being in CCR at 5 years of only .21 possibly because toxicity in these elderly patients sometimes necessitated a reduction of the full treatment. However, even for those patients above 35 years who received the complete treatment the outcome was worse,[2] thus indicating that higher age is in itself an adverse factor in adult ALL.

CNS involvement at diagnosis is regarded as being adverse for remission duration. In contrast to earlier observations,[35,36] the outcome for our 24 patients with initial CNS disease and a disease-free survival probability of .51 at 5 years was even better than that for patients without initial CNS involvement. This somewhat surprising result may be partly because the majority of these patients belonged to the low-risk group, but it may also have implications for CNS treatment in the study. Patients with CNS involvement at

diagnosis were treated with intrathecal methotrexate until the spinal fluid was cleared of blast cells and thereafter; in addition, they received irradiation of both the skull and neuroaxis with 30 Gy. This CNS treatment is apparently more successful in prolonging remission than the prophylactic CNS treatment in the protocol that consisted of 24-Gy skull irradiation and only four intrathecal doses of methotrexate. The CNS prophylaxis has therefore been intensified in the ongoing study.

Within this adult ALL study it could be shown that the remission duration is strongly correlated ($P = .0001$) to the number of adverse prognostic factors in an individual patient. This type of analysis also permitted an assessment of the importance of single adverse factors in adult ALL patients. The adverse factors age above 35 years and elevated leukocyte count caused a very similar relapse pattern, whereas that for the small group with late CR as their only adverse factor suggests that there are two patient populations, one that apparently has poor remission quality and relapses immediately after the end of induction therapy and another without further relapses over the whole observation period and a probability of being in CCR of .45. Here, because no predictive criteria were found to differentiate between the two groups, methods for detection of minimal residual disease are needed to decide which patients require further treatment. When patients with any one of the adverse factors high leukocyte count, older age, or late CR have in addition other adverse factors, their outcome is worsened, significantly for those with a high leukocyte count (Table 5).

Similarly, it was possible to assess the outcome for patients with a given immunologic subtype and how it is influenced by adverse prognostic factors. Patients with the subtypes c-ALL and T-ALL without adverse factors have a fairly good prognosis, with CCR rates of .57 and .73, and actually the outcomes for patients with these subtypes alone are not so different. However, for the patients with c-ALL or T-ALL who also have adverse prognostic factors, it is evident that c-ALL is particularly badly affected, and a high leukocyte count has the major impact. For the heterogeneous group of null-ALL patients the remission duration is equally inferior for those with and for those without other adverse prognostic factors, which indicates that the poor outcome is determined by the subtype itself.

In conclusion, from this and other recent adult ALL studies with intensive therapy, similar prognostic factors for disease-free survival such as leukocyte count, age, time required to achieve CR, immunologic subtypes, and karyotype emerge.[15,24-26] It may well be unjustified to apply these factors in other studies with different treatment schedules, but within a study they are certainly useful to define risk groups, as have already been established in childhood ALL. The present study allows a stratification into low-risk and high-risk patients. The continuous disease-free survival rate of .62 for the low-risk patients is very promising, and thus their treatment protocol in the subsequent study has only minor changes. For the high-risk patients, however, with a disease-free survival rate of .28, the chemotherapy has been further intensified, and they are, in addition, allocated to allogeneic or autologous bone marrow transplantation in first remission.

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