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Intensive Therapy and Prognostic Factors in Acute Lymphoblastic Leukemia of Childhood: CCG 141

A report from Childrens Cancer Study Group*

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A. Introduction

Studies reported by CCSG (Miller et al. 1974; Robison et al. 1980), other cooperative groups (George et al. 1973), and independent pediatric cancer centers (Simone 1976) have clearly indicated that front-end prognostic factors can be as important, or more important, than the therapy itself in determining the results of a modern clinical trial in previously untreated children with acute lymphoblastic leukemia (ALL). This effect becomes even more pronounced as the majority of patients are surviving free of disease for 5 or more years. Definitive results of clinical trials may require 5 to 7 years of follow up to determine the optimal duration of therapy or even longer to determine the rate of long-term survival.

Treatment strategies using multiple-drug induction and maintenance therapy, central nervous system (CNS) prophylaxis, and intensive supportive care have resulted in complete remission rates of 90%–95% or greater and disease-free survival of 5 years or more in 50%–60% of all patients. Because treatment interacts with host and disease, this study, CCG 141, was launched in 1975 to evaluate prognostic factors that influence induction rate, duration of complete continuous remission (CCR), and survival and to identify subsets of patients with a high risk of early failure or with a particularly favorable prognosis. The efficacy of more intensive induction and maintenance therapy was evaluated in patients with a poor prognosis based upon initial white blood cell (WBC) count.

The purpose of this report is to present the results of the treatment regimens and to redefine prognostic groups based upon the prospective evaluation of front-end factors.

B. Materials and Methods

I. Patients

Previously untreated children under 20 years of age were eligible for this study. Informed consent in accordance with institutional policies approved by the U.S. Department of Health, Education, and Welfare was obtained prior to entry on study. Criteria for response to therapy and status of disease were those used by the Childrens Cancer Study Group (CCSG). Remission status of the bone marrow was determined by the per cent of blasts ($<5\%=M_1$, $6\%–25\%=M_2$, $>25\%=M_3$). The prognostic groups, i.e., "low risk," "average risk," and "poor risk," are defined by age and WBC at diagnosis as presented by Nesbit et al. (1979) and currently in use by CCSG.

II. Special Determinations

Stained and unstained bone marrow slides or cover slips were evaluated using a modification of the FAB classification (Bennett et al. 1976; Miller et al., to be published). Quantitative immunoglobulins G, A, and M were performed by the methods of Fahey and McKelvey (1965).

III. Therapy Regimens

The study schema is presented in Fig. 1, and the dosage schedule in the treatment regimens is listed in Table 1. Patients were assigned to two treatment groups i.e. the "low" (initial institutional WBC less than 20×10^9/l) (LR_1) or "high" group (initial WBC equal to or greater than 20×10^9/l, and/or mediastinal widening on chest PA; and lateral, Bucky films

* Principal investigators of CCSG and their grant support are listed in the acknowledgments

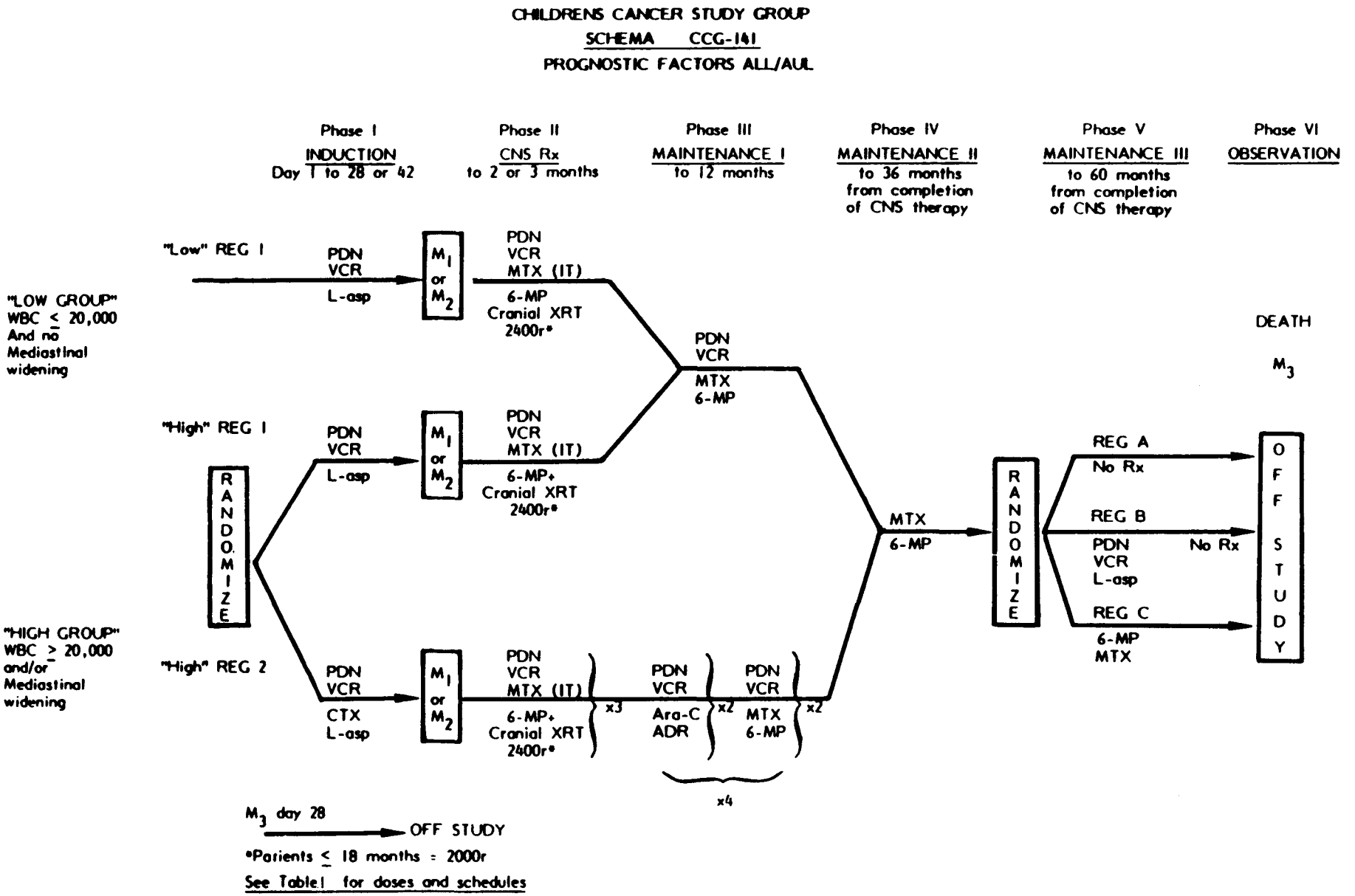

Fig. 1 Schema of CCG 141

Table 1. Dosage schedule of treatment regimens

Group	Induction	CNS-RX	Maintenance I	Maintenance II AND III
"Low" "High"	Reg. 1[a] PDN 40mg/m^2 q d p.o. VCR 1.5mg/m^2 q wk IV L-Asp 6000 IU/m^2 IM tiw (9 doses)	Reg. 1[a] PDN 40mg/m^2 q d×5 q mo p.o. VCR 1.5mg/m^2 q mo IV IT MTX 12mg/m^2 q wk×6 6-MP 75mg/m^2 q d p.o. +2400r Cranial XRT[b]	Reg. 1[a] PDN 40mg/m^2 q d×5 mo p.o. VCR 1.5mg/m^2 q mo IV MTX 20mg/m^2 q wk p.o. 6-MP 75mg/m^2 q d p.o.	MTX 20mg/m^2 q wk p.o. 6-MP 75mg/m^2 q d p.o. for 2 yrs. (4 yrs in Maint. III, Reg. C)
"High"	Reg. 2[a] Same as Regimen 1, plus Cytoxan 100mg/m^2 q d p.o.	Reg. 2[a] POMP-I PDN 40mg/m^2 q d×4 p.o. VCR 1.5mg/m^2 q mo IV)q IT-MTX 12mg/m^2 d-1&4) 14d 6-MP 500mg/m^2 p.o. q d 4)×3 +2400r Cranial XRT[b] After 42 days, Maintenance I therapy is begun.	Reg. 2[a] POCA PDN 40mg/m^2 q d×4 p.o. VCR 1.5mg/m^2 q 21 d IV ADR 40mg/m^2 q 21 d IV Ara-C 100 mg/m^2 q d×4 IV, IM, SQ, q 21 d twice POMP PDN 40mg/m^2 q d p.o. VCR 1.5mg/m^2 q mo IV MTX 5 mg/m^2 q d×4 p.o. 6-MP 500mg/m^2 q d×4 p.o. every 14 days twice.	MTX 20mg/m^2 q wk p.o. 6-MP 75mg/m^2 q d p.o. for 2 yrs. (4 yrs in Maint. III, Reg. C)

[a] Refer to Schema (Fig. 1) for group, phase, and regimen
[b] Patients≤months of age receive 2000r

and/or tomography). "High" patients were randomly assigned to either "High Regimen 1" (HR_1) or "Regimen 2" (R_2).

In May 1976 after the results of CCG 101 indicated that mediastinal mass was not an independent prognostic factor, patients were no longer stratified on the basis of presence or absence of mediastinal mass. At that time five patients with initial WBC $<20\times10^9$/l had been randomized to either HR_1 or R_2. Patients with M_1 marrow on day 28 or M_1 or M_2 marrow on day 42 advanced to CNS prophylaxis which consisted of 2400 rads to the cranium and intrathecal (IT) methotrexate (MTX) as 12 mg/m^2 weekly for 6 weeks (HR_1) or twice weekly for 3 weeks (R_2). Pulses of vincristine (VCR) and prednisone (PDN) were dropped during Maintenance II. At 36 months from completion of CNS therapy, patients in complete continuous remission were randomized to receive either no further therapy (Reg. A), a 4-week reinduction with PDN, VCR, and L-asparaginase (LASP) (Reg. B), or continued maintenance therapy with 6-mercaptopurine (6-MP) and MTX for 2 more years (Reg. C). All males underwent bilateral testicular open-wedge biopsies prior to randomization to Maintenance III.

Patients were considered off study for the following reasons: M_3 marrow on day 28 or any time during CNS or maintenance phases, death, severe toxicity, major protocol violation, or loss to follow-up. Patients experiencing an extramedullary relapse were reinduced with PDN, VCR, LASP, and IT MTX and were restarted on maintenance at the point of relapse. CNS relapse was treated with IT MTX and an additional 2400 rads of cranial and 1200 rads spinal irradiation. Testicular relapse was treated with 2000 rads bilateral testicular irradiation.

C. Biostatistical Considerations

The log rank method of life table analysis (Peto et al. 1977) was used to evaluate the relative relapse rates or death rates for the treatment regimens and to determine the importance of

prognostic characteristics under investigation. The Cox regression model (1972) for life table data was used in the multivariate analysis of prognostic factors determined to be of significance in the univariate analysis.

Complete data required to redefine prognostic groups were available on 360 (40.8%) of the 882 eligible patients. The age and WBC characteristics of the patients with incomplete data (59.2%) are similar to those for whom complete data were available.

D. Results

I. Progress

A total of 911 patients were registered on study, of whom 29 were ineligible (wrong diagnosis-ANLL, prior antileukemic therapy, clinical data and flow sheets never submitted). Of the 882 eligible patients, 576 were entered oni LR_1, 151 on HR_1, and 155 on R_2. The clinical characteristics of the patients entered on study are presented in Table 2. The median followup is over 36 months for all patients entered on study.

II. Inductions

The rates of complete remission (M_1 marrow) for all eligible patients entered on LR_1, HR_1, and R_2 were 95%, 93%, and 91%, respectively. A total of 827 patients (93.8%) completed induction with an M_1 marrow by day 28 or 42, and 832 (94.3%) were entered on the CNS therapy phase, five of whom had M_2 bone marrow ratings. Significant unfavorable factors of response to induction therapy, as determined by univariate analysis, were age >10 years, initial WBC $>20\times10^9$/l, presence of CNS disease at diagnosis, L_2 and L_3 morphology, decreased IgG, Down's syndrome, and <30% PAS positive lymphoblasts. Marrow status on day 14 of induction was also a significant predictor in that 99.7% (454/455) of children with an M_1 bone marrow on day 14 were M_1 at completion of induction, and only 81.4% (57/70) with M_3 marrow on day 14 were M_1 on day 28 or 42 of induction. Children over 10 years of age with initial WBC $>20\times10^9$/l and depressed IgG had a complete remission rate of only 55%.

Using multivariate regression analysis in a subset of 319 patients in whom complete data

Table 2. Clinical characteristics of eligible patients entered on CCG-141

Characteristic	%		%
Age, years		*FAB Morphology*	
<1.5	6	L_1 (>75% L_1)	84
1.5–3	18	L_2 (>25% L_2)	15
>3–10	54	L_3	1
>10	22		
WBC ($\times10^{-9}$/liter)		*Immunoglobulins*	
<10	53	Normal	82
10–49	30	Depressed (1 or more)	18
≥50	17		
Low Risk[a]	22.2	*Hemoglobin (gm/dl)*	
Average risk	60.0	<7	43
High risk	17.8	7–10	45
		>10	12
Sex			
Male	57	Massive hepatomegaly	13
Female	43	Massive splenomegaly	14
		Massive adenopathy	7
Race		Lymphoma syndrome	5
White	89		
Non-white	11	Down's syndrome	2
CNS disease at diagnosis	4	M_3 BM, d14	10
Mediastinal mass	7		

[a] As defined by Nesbit et al. (1979)

on all the selected prognostic variables were available, age > 10 years ($P=0.0008$), CNS disease at diagnosis ($P=0.0007$), and depressed IgG ($P=0.004$) were the strongest predictors of induction failure.

III. Duration of CCR

Duration of CCR and hematologic remission is longer and relative relapse rate is lower in children entered on LR_1 than in patients entered on HR_1 and R_2 in which no significant differences are noted (Fig. 2). At 48 months, 65.2%, 48.1%, and 39.1% of patients on LR_1, HR_1, and R_2, respectively, remain in CCR. When HR_1 and R_2 are analyzed by average and high risk prognostic groups as defined by Nesbit (1979) no superiority of either regimen is observed. Of the patients completing induction, 57.6% remain in CCR.

IV. Maintenance II

During Maintenance II pulses of monthly PDN and VCR were deleted. No significant differences in relative relapse rates in the three regimens were observed (0/E 0.91, 1.14, 1.35 in LR_1, HR_1, and R_2, respectively, $P=0.16$). When compared to the previous CCG trial (CCG 101/143) in which monthly pulses of PDN and VCR were given throughout maintenance, no significant differences are apparent when data in comparable prognostic groups are compared (Fig. 3).

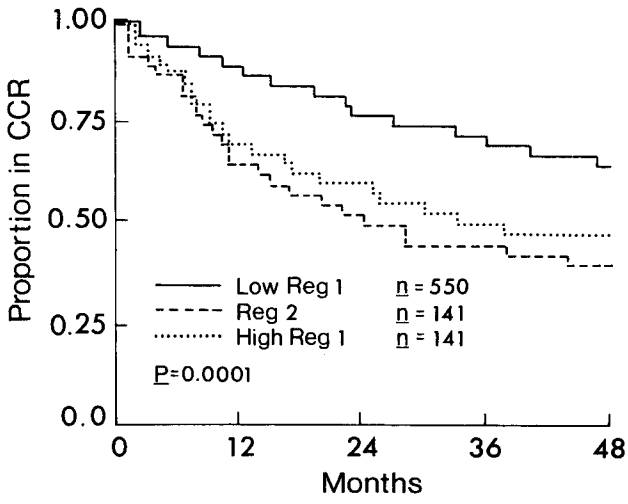

Fig. 2. Duration of complete continuous remission from start of CNS therapy by treatment regimen. First events include bone marrow or extramedullary relapses or death

V. CNS Relapse

The incidence of isolated CNS relapse in LR_1, HR_1, and R_2 is 4.7%, 8.5%, and 12.8%, respectively. These differences are significant (0/e=0.66, 1.46, 2.36, $P=0.001$). In all patients successfully completing induction, the overal CNS relapse rate is 6.7%.

VI. Testicular Relapse

During maintenance therapy, testicular relapse has occurred in 44 boys, or 9.6% of 459 patients at risk. The testicular relapse is

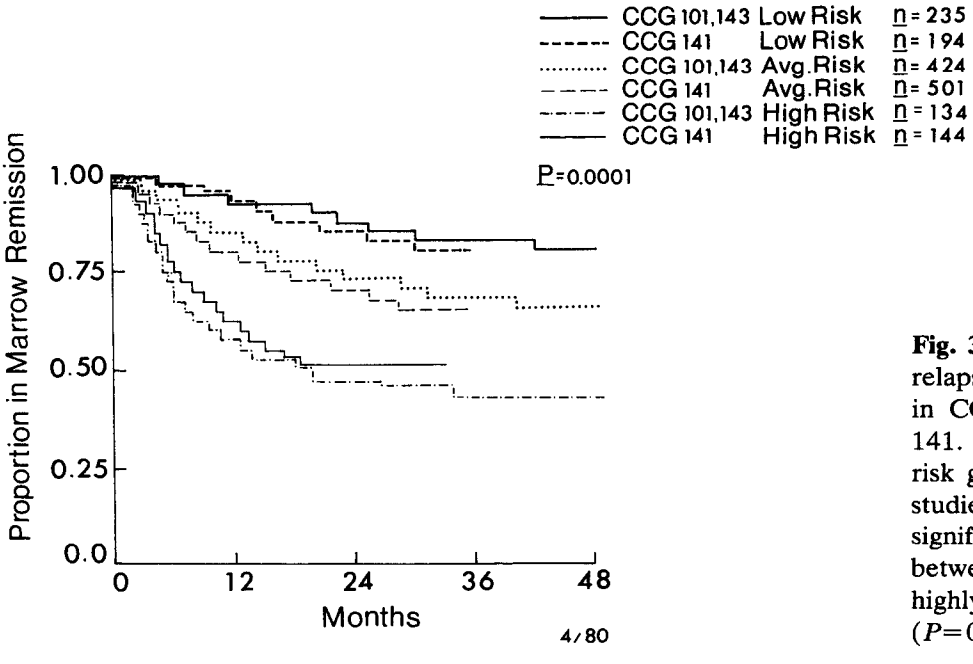

Fig. 3. Rate of bone marrow relapse by prognostic groups in CCG 101/143 and CCG 141. The differences within risk groups between the two studies are not statistically significant. The differences between the risk groups are highly significant ($P=0.0001$)

significantly higher in HR_1 (14.5%, 0/E 1.84) than in R_2 (7.4%, 0/E 0.98) or LR_1 (8.9%, 0/E=0.85) (P=0.047).

VII. Survival After First Isolated Relapse

Isolated bone marrow, CNS, and testicular relapses have occurred in 204, 57, and 34 patients, respectively. Despite reinduction therapy and prophylactic IT MTX in patients experiencing extramedullary relapses, the median survival after isolated testicular and CNS relapse was 19 months and 22 months, respectively. Median survival after first bone marrow relapse occurring predominantly in high risk patients during the first 24 months of therapy was only 10 months (Fig. 4).

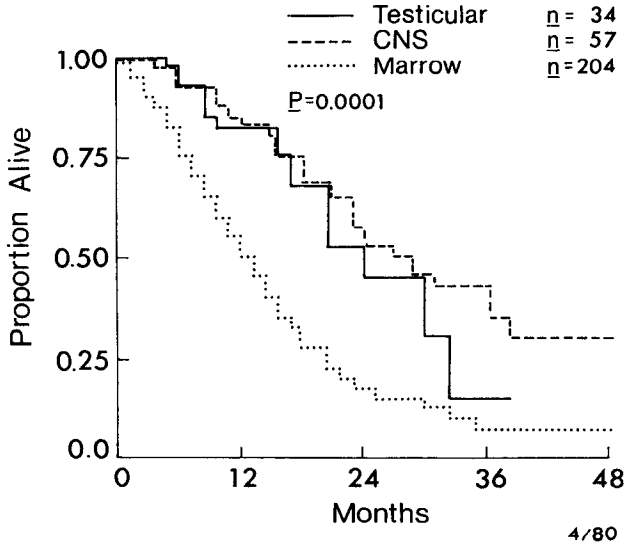

Fig. 4. Survival after first isolated relapse by type of first relapse

Table 3. Significant variables for predicting disease-free survival in CCG-141[a]

Rank	Variable	Significance Level (P-Value)
1	log WBC	0.002
2	Hemoglobin	0.005
3	IgM	0.005
4	Splenomegaly	0.007
5	Age and Age^2	0.040 & 0.014
6	Day 14 marrow	0.029
7	Sex	0.036
8	IgG	0.070
9	Morphology	0.090

[a] Platelet count, CNS disease at diagnosis, nodal enlargement, mediastinal mass status, race, IgA, and hepatomegaly were not significant predictors of outcome in a multivariate context

VIII. Prognostic Factors

1. Disease-Free Survival (CCR)

Using the Cox regression model for life table data, significant variables for predicting disease-free survival were identified (Table 3). In rank order these are:

1. Log WBC
2. Hemoglobin
3. IgM
4. Splenomegaly
5. Age and age^2
6. Day 14 bone marrow and
7. Sex

IgG and FAB morphology were of borderline significance (P=0.07 and 0.09). Platelet count, CNS disease at diagnosis, lymph node enlargement, mediastinal mass, race, IgA, and hepatomegaly were not significant predictors of disease-free survival. Using this multivariate analysis, we established new definitions of good, average, and poor prognosis (risk) groups (Table 4). Good prognosis patients have all favorable factors; poor prognosis patients have one or more unfavorable characteristics. Average prognosis patients comprised the remainder. Using these criteria, good, average, and poor prognosis groups comprised 28.1%, 50.8%, and 21.1%, respectively, of the entire patient population. The 48-month CCR rates in the three groups, excluding infants <1 year, are 92.1%, 55.4%, and 45.7%, respectively (Fig. 5). The 48-month survival rates for the three groups are 93.9%, 61.6%, and 20.8% (not shown).

2. Survival

A different rank order of factors predicting survival from *entry on study* was determined. Log WBC, IgG, age (age^2), and FAB morphology were significant predictors (P=<0.05), and IgM, CNS disease at diagnosis, and hemoglobin were of borderline significance (P 0.06–0.159) as predictors of survival (Table 5).

E. Discussion

Generally, the outlook in "high risk" or poor prognosis ALL associated with early relapse

Factor	Prognostic group		
	Good	Average	Poor
WBC×10^9/l	<20	20–100	>100
Age, yrs.	2–10	>10	<1
Lymphoma syndrome	(0)	(<3)	(3 or more)
Hgb, gm/dl	<10		>10
L,S,N	Not markedly enlarged		Markedly enlarged
Mediastinal mass	Absent		Present
CNS disease at Dx	Absent	Absent	Present
FAB morphology	≥75% L_1	≥75% L_1	≥25% L_2
Ig, depressed	0–1	0–3	
BM d14	M_1 or M_2	$M_{1,2,3}$	

Table 4. Favorable and unfavorable characteristics

and death remains bleak despite efforts to improve the duration of disease-free and overall survival in this subset of patients accounting for approximately 20%–25% of childhood ALL. During the past 8 years the duration of disease-free and long-term survival has not changed significantly despite efforts to increase the intensity and perforce the toxicity of therapy. In this study more intensive induction, CNS, and maintenance therapy in poor prognosis patients, defined by initial WBC alone, was no better than standard and much less toxic therapy. Others have observed that intensification of therapy did not achieve better results in patients variously defined as having a poor prognosis (Haghbin et al. 1974, to be published; Aur et al. 1978; Sallan et al. 1980). Future directions in the treatment of childhood ALL will be aimed at decreasing morbidity and late effects of cancer therapy through maximally effective and minimally toxic regimens. This study has identified a subset of patients, comprising 28% of the total, with a projected five-year disease-free survival of >90% (Table 4).

In addition to the important contribution of leukemic thrust or burden as measured by the degree of organomegaly and lymphadenopathy, the hemoglobin level, and the presence of mediastinal (thymic) mass and CNS disease at diagnosis, this study also identified three additional statistically significant favorable prognostic factors–L_1 lymphoblast morphology using a modification of the FAB classification,

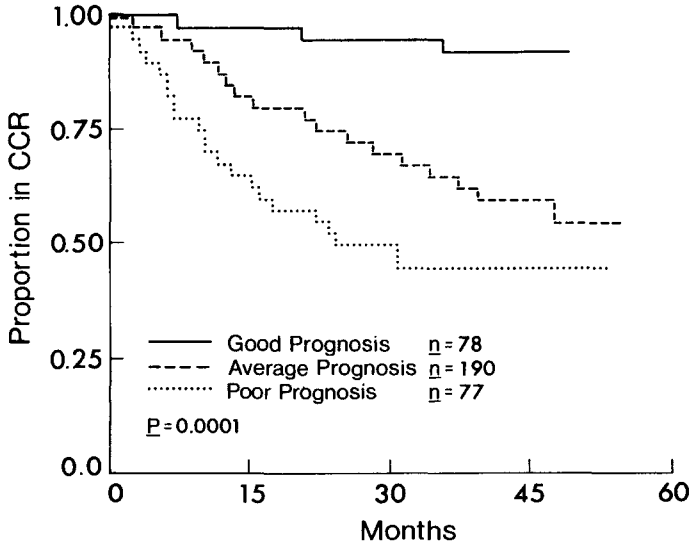

Fig. 5. Complete continuous remission by newly defined prognostic groups (see text). The differences are highly significant ($P=0.0001$)

Table 5. Significant variables for predicting survival from on study in CCG-141[a]

Rank	Variable	Significance Level (P-Value)
1	Log WBC	0.001
2	IgG	0.009
3	Age and age^2	0.038 & .003
4	Morphology	0.048
5	IgM	0.067
6	CNS disease at diagnosis	0.089
7	Hemoglobin	0.159

[a] Platelet count, nodal enlargement, splenomegaly, hepatomegaly, sex, mediastinal mass status, and race were not significant predictors of outcome in a multivariate context

normal or elevated immunoglobulin levels, and M_1 bone marrow status on day 14 of induction therapy. Detailed accounts of the prognostic significance of FAB morphology (Miller et al., to be published) and immunologic factors (Leikin et al., to be published) are presented in companion papers. Others (Jacquillat et al. 1974; Frei and Sallan 1978) have found that rapid lysis of bone marrow blasts and restoration of normal hematopoiesis are associated with a good prognosis. Failure to respond promptly to induction therapy implies the rapid emergence of drug resistant cells, misdiagnosis, or inadequate therapy. Monitoring of the initial response to induction therapy appears warranted so that modification of induction therapy can be introduced early in treatment and assure the best possible chance of complete remission. Despite the excellent remission rates achievable with current therapy, the relapses occurring early in maintenance suggest that the accepted definition of complete remission requires revision and that more accurate and quantitative methods to determine the residual leukemic population are needed. Techniques such as terminal deoxynucleotidyl transferase, cytofluorometry, use of monoclonal antibodies, and cytogenetic markers may be helpful.

Immunoglobulin G ($P=0.009$) and lymphoblast morphology ($P=0.048$) were significant for survival but only marginally for disease-free survival ($P=0.07$ and $P=0.09$, respectively). This is probably because decreased IgG and L_2 lymphoblast morphology were associated with a higher probability of induction failure and subsequent death. A similar explanation could account for CNS disease at diagnosis being a stronger predictor of survival than of disease-free survival.

The beneficial role of monthly pulses of PDN and VCR during maintenance therapy has never been determined in a prospective trial. Simone et al. (1975) suggested that monthly pulses of PDN and VCR contributed to immunosuppression and more infectious disease complications without improving the overall therapeutic results. In CCG 141 pulses of PDN and VCR were discontinued after 12 months in all patients. When the data in CCG-141 were compared to those obtained in the two previous CCSG studies (CCG 101,143) no statistically significant differences in duration of hematologic remission (Fig. 3), disease-free survival or overall survival are noted, suggesting that VCR-PDN pulses may not be required during maintenance.

Patients experiencing an isolated bone marrow, testicular, or CNS relapse were at high risk of early death with median survivals after the first relapse of 10, 19, and 22 months, respectively. The relatively short survival after isolated extramedullary relapse occurred despite reinduction with PDN, VCR, and LASP and prophylactic or specific retreatment to the CNS. These results suggest that more intensive reinduction and maintenance programs are required in patients experiencing isolated extramedullary relapses. Bone marrow transplantation is an alternative approach for patients sustaining an early bone marrow relapse and is now being studied by CCSG.

The data generated by this study have defined new prognostic groups based upon clinical, morphologic, and immunologic features and will be used to design the new generation of ALL protocols. A key feature of the new studies will be to reduce further the acute and late toxic effects of therapy in patients with a good prognosis and to improve upon the 45% disease-free survival of children with a poor prognosis.

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