



Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983–1995

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Since 1968, the Children's Cancer Group (CCG) has treated more than 16 000 children with acute lymphoblastic leukemia (ALL). Herein, we report improvements obtained in CCG trials during two successive series of studies (1983–1988 and 1989–1995). Overall, 10-year EFS was 62% ± 10% for the 1983–1988 series and 72% ± 1% for the 1988–1995 series ($P < 0.0001$). Five-year cumulative rates of isolated CNS relapses were 5.9% and 4.4%. Therapy based on the Berlin–Frankfurt–Münster 76/79 study improved outcomes for intermediate and higher risk patients in the first series. For intermediate risk patients, delayed intensification (DI) was most crucial for improved outcome and cranial irradiation was safely replaced with maintenance intrathecal methotrexate, providing patients received intensified systemic therapy. In the second series, randomized trials showed better outcome with one vs no DI phase for lower risk patients, with two vs one DI phase for intermediate risk patients, and with the CCG 'augmented regimen' for higher risk patients with a slow day 7 marrow response. Cranial irradiation was safely replaced with additional intrathecal methotrexate for higher risk patients with a rapid day 7 marrow response. In a subsequent study, substitution of dexamethasone in place of prednisone in induction and maintenance improved outcome for standard risk patients. All patients received dexamethasone in DI. These successful treatment strategies form the basis for our current ALL trials. *Leukemia* (2000) 14, 2223–2233.

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Introduction

The Children's Cancer Group (CCG) is an association of more than 120 centers in the United States, Canada, and Australia. More than 16 000 infants, children and adolescents have enrolled on CCG trials for acute lymphoblastic leukemia (ALL) since 1968. The 5-year event-free survival (EFS) has increased from less than 10% in earliest efforts to more than 80% in projections from current trials. In the 1970s, we adapted effective presymptomatic central nervous system (CNS) therapy, pioneered by St Jude Children's Research Hospital.^{1,2} Subsequently, we demonstrated that cranial irradiation and intrathecal methotrexate might replace cranial spinal irradiation^{3,4} and that 18 Gy cranial irradiation might replace 24 Gy⁵ with similar efficacy. We also developed a widely adopted dosage schedule for intrathecal methotrexate that improved efficacy and decreased neurotoxicity.⁶

In the 1980s, we adapted the strategy of effective post-induction intensification, originally pioneered by Riehm, Henze, and colleagues in the Berlin–Frankfurt–Münster Group (BFM),^{7,8} for use in CCG protocols.^{9,10} The BFM investigators showed the value of post-induction intensification for lower risk patients.¹¹ However, patients received intensive induction

consolidation. Our randomized trials extended these observations by demonstrating that NCI/Rome standard risk^{12,13} patients who received post-induction intensification derived no added benefit from intensive induction-consolidation,¹⁴ but did derive further benefit from two courses of post-induction intensification.¹⁵ We also demonstrated the value of longer and stronger post-induction intensification for higher risk patients with a poor early marrow response.¹⁶

In this report, we provide long-term outcome for 8832 patients on CCG risk-adjusted trials for ALL conducted during two successive series of studies spanning the period 1983–1995.

Methods

Between 1983 and 1988, a total of 3801 patients were entered on the CCG-100 series of studies: 3713 (98%) were eligible and 90 (2%) were ineligible. The most common reason for ineligibility was lack of adequate approval by the local Institutional Review Board. Two eligible patients lacked follow-up data and are not included in this analysis, resulting in a final cohort of 3711 patients. Patients were stratified by age, white blood cell count (WBC), gender, platelet count, FAB classification,^{17–19} and lymphomatous features.^{20,21} The 'lowest risk' patients received vincristine, prednisone, and L-asparaginase during induction, intrathecal methotrexate in induction, consolidation, and maintenance, and daily oral 6-mercaptopurine, weekly oral methotrexate, and monthly vincristine/prednisone pulses in maintenance on CCG-104. 'Intermediate risk' patients were randomly allocated to receive standard or intensive induction/consolidation, delayed intensification (DI) or no intensification, and 18 Gy cranial irradiation or 12-weekly doses of maintenance intrathecal methotrexate on CCG-105.^{14,22} 'Higher risk' patients with lymphomatous features²⁰ were randomly allocated to LSA₂L₂ with or without cranial irradiation, the New York (NY) I regimen, or the CCG modified BFM regimen⁹ on CCG-123.^{20,21} 'Higher risk' patients without lymphomatous features were randomly allocated to the standard CCG regimen, NYI, or the CCG-modified BFM regimen⁹ on CCG-106.^{10,23} Infants were treated on CCG-107, which employed very high-dose methotrexate (33.6 g/m²) with leucovorin rescue.²⁴

Between 1989 and 1995, a total of 5185 patients were entered on the CCG-1800 series of studies: 5121 (99%) were eligible and 64 (1%) were ineligible. The most common reason for ineligibility was lack of unconditional approval by the local Institutional Review Boards. Patients were stratified by age, WBC, gender, platelet count, and lymphomatous features. 'Lower risk' patients were randomly allocated to receive DI or not on CCG-1881.²⁵ 'Intermediate risk patients', now excluding anyone 10 years of age or older, all received a single DI phase and were randomly allocated to receive

vincristine/prednisone pulses every 4 weeks, vincristine/prednisone pulses every 3 weeks, or a second DI phase and vincristine/prednisone pulses every 4 weeks on CCG-1891.¹⁵ Upon completion of these initial studies in 1992 and 1993, subsequent NCI/Rome standard risk patients were enrolled on CCG-1922, which compared oral vs parenteral 6MP and dexamethasone vs prednisone in induction and maintenance. All patients received dexamethasone during a single DI phase.²⁶ All patients on these three trials received maintenance intrathecal methotrexate and cranial irradiation was reserved for those with overt CNS disease at diagnosis.

'Higher risk' patients with lymphomatous features²⁰ were randomly allocated to NYI or NYII therapy^{27,28} on CCG-1901. 'Higher risk' patients with WBC $\geq 50\,000/\mu\text{l}$ or age ≥ 10 years who lacked lymphomatous features were assigned to CCG-1882.^{16,29,30} On CCG-1882, patients with no CNS disease at diagnosis (<5 leukocytes/ μl or no blasts in the cerebrospinal fluid) and $<25\%$ marrow blasts on day 7 of an induction phase consisting of vincristine, prednisone, L-asparaginase, and daunomycin were randomly allocated to receive 18 Gy cranial irradiation or additional intrathecal methotrexate. Patients on CCG-1882 with $\geq 25\%$ marrow blasts on day 7 of induction were initially treated on a pilot study of an augmented regimen.²⁹ After this initial phase demonstrated the safety of the augmented regimen, such patients were randomly allocated to our standard CCG-modified BFM regimen or to our augmented regimen.¹⁶ Infants <1 year of age were treated on CCG-1883²⁴ and received intensive induction, consolidation including very high-dose methotrexate (33.6 g/m^2), and intensive post-consolidation therapy, without cranial irradiation.

Classification as B-precursor and T-lineage was determined centrally in the CCG ALL Reference Laboratory. Cases with $>30\%$ CD7 positivity were classified as T-lineage and cases with $>30\%$ CD19 positivity were classified as B-precursor.³¹ Diagnostic karyotyping of leukemic cells was performed by institutional laboratories prior to initiation of therapy. Aberrations were designated according to ISCN criteria.³² Designation of an abnormal clone required the identification of two or more metaphase cells with identical structural abnormalities or identical extra chromosomes, or three or more metaphase cells with identical missing chromosomes. A 'normal' case required complete analysis of a minimum of 20 banded metaphase bone marrow cells. Between 1988 and 1995, a total of 5121 children were entered on the CCG studies described above. Among these, 1946 cases (38%) had centrally reviewed and accepted cytogenetic data.

Statistical methods

Standard life table methods³³ and associated statistical tests were employed for analysis of outcome. EFS from study entry was defined as the probability of surviving without induction death or failure, remission death, relapse, or second malignancy measured from study entry. EFS from post-induction randomization time points was defined as the probability of surviving without a remission death, relapse, or second malignancy, and was measured from the time of randomization. Among the studies included in this analysis, only the CCG-1881 and CCG-1882 studies used post-induction randomization; in all other studies, randomization was done at study entry. Overall life table results represent EFS from study entry, whereas regimen comparisons are EFS from randomization. Patients without adverse events were censored on the date of

last reported contact. Life table comparisons of EFS outcome between patient groups used the log rank statistic.^{34,35} Therefore, *P*-values are based on the pattern of outcome across the entire period of patient follow-up and assume proportional hazards. The standard deviation (s.d.) of the life table estimates used a Peto variance calculation.³⁵ Approximate 95% confidence intervals can be obtained for point estimates of EFS from the life table value ± 1.96 standard deviations. Life table results for cause-specific occurrence of isolated CNS relapse or concurrent CNS relapse as an initial event used the method of cumulative incidence function estimates.³⁶

Long-term follow-up was assessed biannually (1983–1989) and annually (1989–1995) via requests sent to institutions. Among the 3711 patients on the CCG-100 series, 2022 remain alive, 969 died, and 720 were lost to follow-up. For 93% of patients not designated as lost to follow-up, the most recent follow-up data were received within the last 36 months. Among the 5121 patients on the CCG-1800 series, 4033 remain alive, 836 died, and 252 were lost to follow-up. For 98% of the 1800 series patients not designated as lost to follow-up, the most recent follow-up data was received within the last 36 months.

Results

Figure 1 displays EFS and survival for 3711 patients on the CCG-100 series conducted between 1983 and 1988 and for 5121 patients on the CCG-1800 series trials conducted between 1989 and 1995. Overall EFS estimates were $65\% \pm 8\%$ at 5 years and $62\% \pm 10\%$ at 10 years for the CCG-100 series. Overall EFS estimates at 5 and 10 years for patients treated on the CCG-1800 series were $75\% \pm 1\%$ and $72\% \pm 1\%$. An approximate 60% of patients on the CCG-100 series studies and 30% of patients on the CCG-1800 series received cranial irradiation. On the CCG-100s, the 5-year overall cumulative rate of an isolated CNS relapse was 5.9%

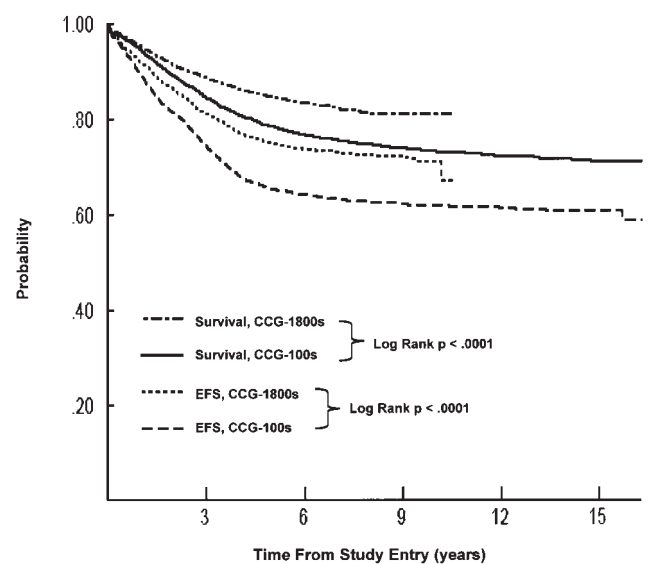


Figure 1 Long-term outcome on CCG trials for childhood ALL during two consecutive treatment eras. Probability of EFS and overall survival from study entry for children treated on the CCG-100 series (1983–1988; $n=3711$) and the CCG-1800 series (1989–1995; $n=5121$) of childhood ALL trials.

and the rate for all CNS relapses was 7.7% (Figure 2a). On the CCG-1800 series, the 5-year overall cumulative rate of an isolated CNS relapse was 4.4% and the rate for all CNS relapses was 5.7% (Figure 2b).

Outcomes for various patient subsets on the CCG-100 series (1983–1988) are shown in Table 1. Adverse prognostic factors in univariate analyses included age <1 year or ≥10 years, male sex, black race, T-lineage immunophenotype, poor early marrow response, and higher WBC count. Trend for poorer outcome with increasing WBC is seen. Day 14 marrow status was assessed for patients on the CCG-105 study and both day 7 and day 14 marrow status were assessed for patients on CCG-123 study. For these studies, EFS according to day 7 or day 14 marrow status was analyzed for the subset of patients achieving remission at the end of induction therapy. On day 7, 59%, 15%, and 25% of patients had M1 (<5% blasts), M2 (5–25% blasts), and M3 (>25% blasts) marrow status, respectively, and 5-year EFS estimates for these groups were 75% (s.d. = 4%), 47% (s.d. = 9%), and 45% (s.d. = 7%), respectively. On day 14, 90%, 7%, and 3% of patients had M1 (<5%

Table 1 Long-term EFS outcome on CCG Trials for childhood ALL (1983–1988)

	Number of patients	5-year EFS ± s.d. (%)	8-year EFS ± s.d. (%)	10-year EFS ± s.d. (%)
All patients	3711	65 ± 8	63 ± 9	62 ± 10
Infants	98	33 ± 5	32 ± 5	32 ± 6
Higher risk ^a	1389	58 ± 1	55 ± 2	55 ± 2
Standard risk ^a	2224	71 ± 1	69 ± 1	68 ± 1
B-lineage	1280	68 ± 1	65 ± 2	64 ± 2
Infants	25	NA ^b	NA	NA
Higher risk	444	62 ± 2	59 ± 3	58 ± 3
Standard risk	811	72 ± 2	69 ± 2	68 ± 2
T-lineage	319	60 ± 1	58 ± 3	58 ± 5
Infants	5	NA	NA	NA
Higher risk	213	58 ± 4	56 ± 4	56 ± 5
Standard risk	100	68 ± 5	65 ± 5	65 ± 6
Gender				
Male	2194	63 ± 1	60 ± 1	59 ± 1
Female	1517	69 ± 1	67 ± 1	67 ± 1
Age				
<1 year	98	33 ± 5	32 ± 5	32 ± 6
1–9 years	2786	69 ± 1	67 ± 1	66 ± 1
≥10 years	827	56 ± 2	53 ± 2	52 ± 2
Ethnicity				
White	2870	67 ± 1	64 ± 1	63 ± 1
Black	212	57 ± 4	53 ± 4	51 ± 5
Hispanic	382	61 ± 3	59 ± 3	59 ± 3
Other	181	65 ± 4	62 ± 4	60 ± 5
WBC				
<10 000/μl	1640	70 ± 1	67 ± 1	66 ± 1
10–50 000/μl	1225	66 ± 1	64 ± 2	63 ± 2
50–100 000/μl	358	60 ± 3	59 ± 3	59 ± 3
>100 000/μl	487	52 ± 2	50 ± 3	49 ± 3
CNS at diagnosis				
Yes	88	59 ± 6	59 ± 6	59 ± 6
No	3622	66 ± 1	63 ± 1	62 ± 1
Day 7 marrow ^c				
M1	123	75 ± 4	74 ± 4	72 ± 5
M2	32	47 ± 9	NA	NA
M3	52	45 ± 7	NA	NA
Day 14 marrow ^d				
M1	1378	72 ± 1	69 ± 1	68 ± 2
M2	110	60 ± 5	58 ± 6	57 ± 6
M3	44	34 ± 7		

^aStandard and higher risk refer to NCI/Rome criteria.

^bNA, not applicable; data not shown for cells with fewer than 20 subjects.

^cData collected only for CCG-123 (lymphomatous features).

^dData collected only for CCG-105 (intermediate risk) and CCG-123 (lymphomatous features).

blasts), M2 (5–25% blasts), and M3 (>25% blasts) marrow status, and 5-year EFS estimates for these groups were 72% (s.d. = 1%), 60% (s.d. = 5%), and 34% (s.d. = 7%), respectively.

Progress achieved with specific treatment strategies for the different risk groups in the 1983–1988 era is shown in Table 2. The reported advantage for the CCG-modified BFM regimen for higher risk patients, either without (CCG-106)²³ or with (CCG-123)²¹ lymphomatous features is maintained with longer follow-up (Figure 3a and b). On CCG-106, the 10-year EFS estimates for CCG-modified BFM therapy vs standard therapy are 63% and 42%, respectively (Table 2). Similarly on CCG-123, 10-year EFS estimates for CCG-modified BFM therapy vs LSA₂L₂ therapy with cranial radiation are 67% and 50%, respectively (Table 2). Outcome with NY regimen is

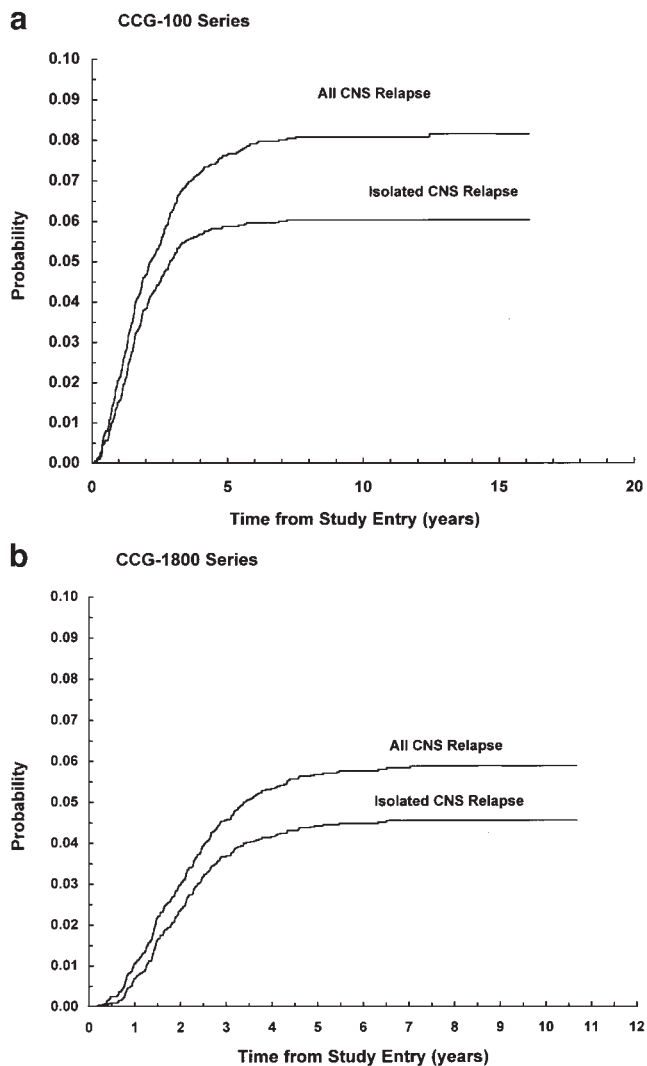


Figure 2 CNS relapse on CCG trials for childhood ALL during two consecutive treatments eras. Cumulative incidence probability of isolated or combined CNS relapses from study entry on (a) the CCG-100 series (1983–1988) of trials; (b) the CCG-1800 series (1989–1995) of trials.

Table 2 Randomized CCG trials (1983–1988) showing improved outcome for children with ALL

Trial	Risk group	n	Intervention and outcome	Change in failure rate
CCG-105	Intermediate (age <10 years)	625	Delayed intensification vs no delayed intensification 10-year EFS of 74% vs 60%	35%
CCG-106	Higher (non-lymphomatous) (age <10 years)	545	BFM vs NYI vs standard therapy 10-year EFS of 63% vs 57% vs 42%	36% ^a
CCG-123	Higher risk (lymphomatous)	694	BFM vs NYI vs LSA ₂ L ₂ 10-year EFS of 67% vs 66% vs 50%	34% ^a

^aBFM vs standard.

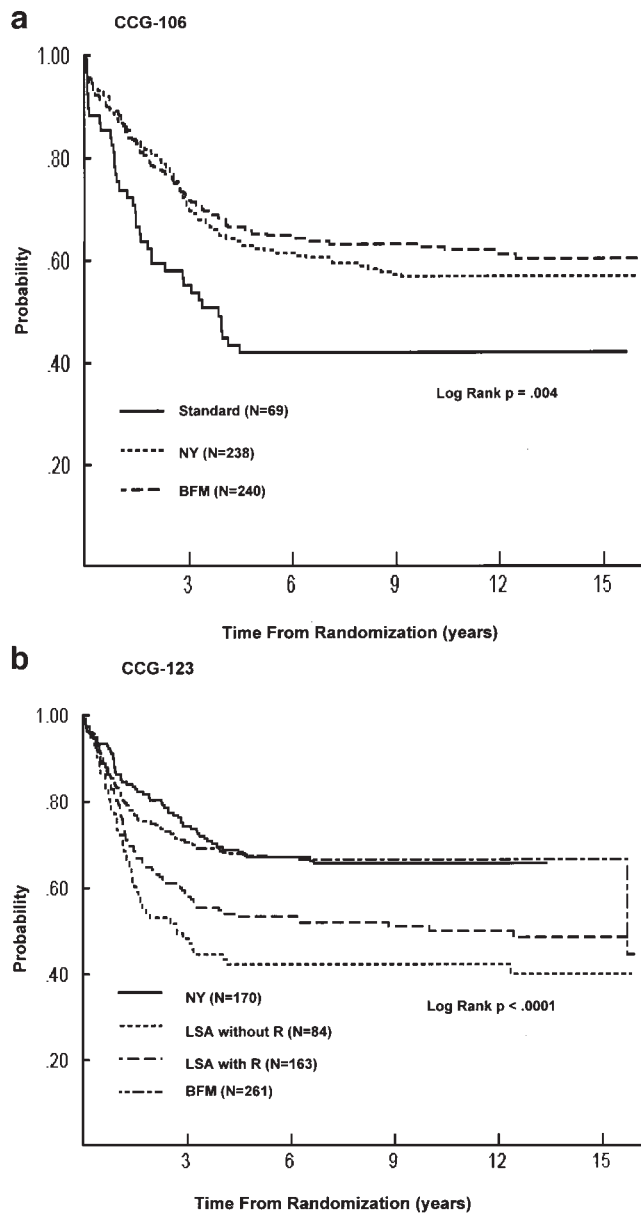


Figure 3 Outcome on CCG trials for higher risk ALL (1983–1988). Probability of EFS from study entry for higher risk patients on (a) the CCG-106 study for those without lymphomatous features; or (b) the CCG-123 study for those with lymphomatous features. R, cranial radiation therapy.

similar to outcome with CCG-modified BFM therapy on both studies.

The overall results of CCG-105 remain as reported.¹⁴ Notably the interesting interaction with age persists as noted in the original report. The benefit of DI vs standard therapy remains evident for patients 1–9 years of age, with 10-year EFS estimates of 74% and 60%, respectively (Figure 4; Table 2). No added benefit of intensive induction consolidation (ie an increase in prednisone dose from 40 mg/m² to 60 mg/m², addition of daunomycin to the initial month of therapy, and addition of cyclophosphamide and cytosine arabinoside to the second month of therapy) is observed for such patients treated with DI. In addition, the finding that better systemic therapy allows replacement of cranial irradiation with maintenance intrathecal methotrexate is maintained with longer follow-up (Figure 5). With only ‘standard’ systemic therapy, the CNS relapse rate is greater than 20% despite maintenance intrathecal methotrexate.²²

CCG-105 also included a number of patients older than 10 years of age. Among this subset, those randomized to both intensive induction/consolidation and DI had a trend toward better outcome than those randomized to DI and standard induction/consolidation ($P=0.06$). Those randomized to receive cranial radiation had better EFS than those assigned to maintenance intrathecal methotrexate alone ($P=0.01$). On

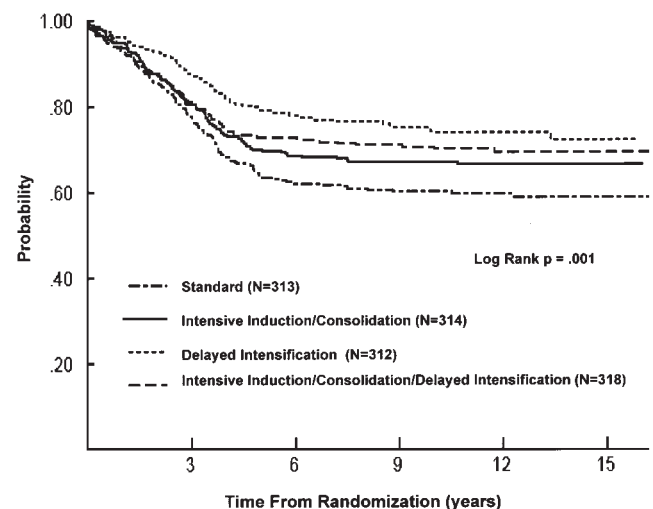


Figure 4 Outcome on the CCG-105 trial for intermediate risk ALL (1983–1988) according to chemotherapy regimen. Probability of EFS from study entry for patients <10 years of age treated with standard therapy or intensive induction/consolidation with or without delayed intensification.

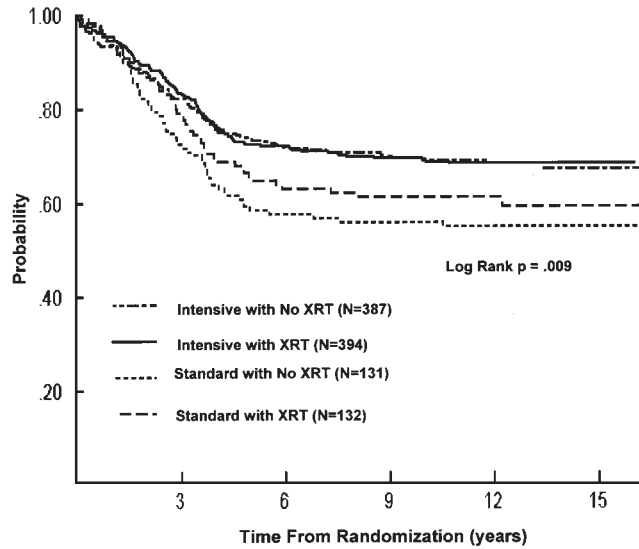


Figure 5 Outcome on the CCG-105 trial for intermediate risk ALL (1983–1988) according to method of CNS prophylaxis. Probability of EFS from study entry for patients <10 years of age treated with standard or intensive (intensive induction/consolidation and/or delayed intensification) chemotherapy and cranial irradiation (XRT) or intrathecal therapy alone (no XRT).

subsequent protocols, such patients are designated higher risk and receive intensive induction consolidation.

Infants treated on CCG-107 had a 4-year EFS of 33%, which represented a significant improvement compared to an EFS of 22% for infants treated on the predecessor studies conducted between 1978 and 1983.²⁴ Longer follow-up reveals a 32% 10-year EFS.

Outcomes for various patient subsets on the CCG-1800 series (1989–1995) are shown in Table 3. Adverse prognostic factors in univariate analyses include age ≥ 10 years, black race, poor early marrow response, abnormal cytogenetics other than hyperdiploidy with more than 50 chromosomes, and higher WBC count. Increasing WBC carries an increasing risk for adverse events. In addition, CNS disease at diagnosis is a significant risk factor in univariate analyses, although it is highly correlated with WBC count in multivariate analyses (data not shown). Day 7 marrow status was reported for patients on all studies except CCG-1881. Among non-infant patients who achieved induction remission, 52%, 23%, and 25% of patients were M1, M2, and M3 on day 7 of induction, and had 5-year EFS estimates of 80% (s.d. = 1%), 74% (s.d. = 2%), and 68% (s.d. = 2%), respectively. The day 7 response had prognostic significance in both standard and higher risk strata.

Findings from several of the CCG-1800 series of studies have been reported thus far only in abstract.^{15,25,26} The value of DI is shown for the subset of patients at lowest risk of relapse defined by age, WBC, gender, platelet count, and early marrow response on CCG-1881. At 5 years, EFS estimates from randomization are 85% and 79%, for the DI and standard regimens, respectively ($P=0.10$; Table 4). The value of double vs single DI is demonstrated for intermediate risk patients on CCG-1891. At 5 years, EFS estimates are 83% and 77% for double and single DI, respectively ($P=0.08$; Table 4). In the succeeding study, CCG-1922, NCI/Rome standard risk patients were randomized to receive either dexamethasone (6 mg/m²) or prednisone (40 mg/m²) in induction and maintenance. All patients received dexamethasone (10 mg/m² \times 21

Table 3 Long-term EFS outcome on CCG trials for childhood ALL (1989–1995)

	Number of patients	5-year EFS \pm s.d. (%)	8-year EFS \pm s.d. (%)	10-year EFS \pm s.d. (%)
All patients	5121	75 \pm 1	73 \pm 1	72 \pm 4
Infants	135	38 \pm 4	37 \pm 6	NA ^b
Higher risk ^a	1841	69 \pm 1	67 \pm 2	67 \pm 9
Standard risk ^a	3145	81 \pm 1	79 \pm 1	77 \pm 5
B-lineage	2883	75 \pm 1	72 \pm 2	71 \pm 6
Infants	86	38 \pm 6	38 \pm 7	NA
Higher risk	931	67 \pm 2	65 \pm 3	NA
Standard risk	1866	80 \pm 1	78 \pm 2	76 \pm 7
T-lineage	431	73 \pm 2	73 \pm 4	73 \pm 20
Infants	2	NA	NA	NA
Higher risk	300	70 \pm 3	70 \pm 5	NA
Standard risk	139	80 \pm 4	79 \pm 7	NA
Gender				
Male	2817	74 \pm 1	72 \pm 2	72 \pm 7
Female	2304	77 \pm 1	74 \pm 2	73 \pm 5
Age				
<1 year	135	38 \pm 4	37 \pm 6	NA
1–9 years	3879	79 \pm 1	77 \pm 1	76 \pm 4
≥ 10 years	1107	66 \pm 2	64 \pm 3	NA
Ethnicity				
White	3834	77 \pm 1	75 \pm 1	75 \pm 4
Black	291	65 \pm 3	63 \pm 7	NA
Hispanic	691	68 \pm 2	67 \pm 4	NA
Other	301	73 \pm 3	71 \pm 5	NA
WBC				
<10 000/ μ l	2530	79 \pm 1	76 \pm 2	75 \pm 4
10–50 000/ μ l	1514	76 \pm 1	75 \pm 2	NA
50–100 000/ μ l	478	70 \pm 2	68 \pm 2	NA
>100 000/ μ l	599	60 \pm 2	59 \pm 4	NA
CNS at diagnosis				
Yes	168	60 \pm 4	59 \pm 8	NA
No	4903	76 \pm 1	74 \pm 1	73 \pm 4
Day 7 marrow ^e				
M1	2026	80 \pm 1	79 \pm 2	NA
M2	913	74 \pm 2	72 \pm 3	NA
M3	969	68 \pm 2	65 \pm 4	NA
Ploidy ^d				
Normal	596	81 \pm 2	80 \pm 3	NA
Hypo <46	114	58 \pm 5	56 \pm 10	NA
45	91	64 \pm 6	62 \pm 11	NA
<45	23	35 \pm 11	35 \pm 28	NA
Pseudo	536	67 \pm 2	65 \pm 4	NA
47–50	206	65 \pm 3	64 \pm 7	NA
>50	494	81 \pm 2	80 \pm 3	NA
Translocations ^d				
Normal	1793	77 \pm 1	75 \pm 2	74 \pm 7
t(4;11)	42	24 \pm 7	NA	NA
t(9;22)	44	26 \pm 9	NA	NA
t(1;19)	67	69 \pm 6	NA	NA

^aStandard and higher risk refer to NCI/Rome criteria.

^bNA, not applicable; data not shown for cells with fewer than 20 subjects.

^cData is from CCG-1922 (standard risk), CCG-1891 (intermediate risk), CCG-1882 (higher risk), and CCG-1901 (higher risk/lymphomatous features); infants on CCG-1883 are excluded; day 7 marrow response was not collected on CCG-1881.

^dData for 1946 patients with accepted cytogenetic data.

days) in DI. At 4 years, EFS estimates are 88% with dexamethasone and 81% with prednisone ($P=0.008$; Table 4). A second randomization comparing oral vs intravenous 6-mercaptopurine shows no difference in EFS.

Results from the CCG-1882 study have been reported in detail.^{16,30} Longer and stronger post-induction intensification (augmented regimen) was introduced for higher risk patients

Table 4 Randomized CCG trials (1989–1995) showing improved outcome for children with ALL

Trial	Risk group	n	Intervention and outcome	Change in failure rate
CCG-1881	Low risk	700	Delayed intensification vs standard therapy 5-year EFS of 85% vs 79%	29%
CCG-1891	Intermediate risk	802	Double vs single delayed intensification 5-year EFS of 83% vs 77%	26%
CCG-1882	Higher risk	310	Augmented BFM vs CCG modified BFM 6-year EFS 72% vs 54%	39%
CCG-1922	Standard	1060	Dexamethasone vs prednisone 5-year EFS of 85% vs 81%	21%

with >25% marrow blasts on day 7 of induction. The benefit of the augmented regimen vs the standard CCG-modified BFM regimen is maintained with further follow-up, with 5-year DFS estimates from randomization of 73% ± 4% and 57% ± 5% ($P = 0.001$; Figure 6; Table 4). Whole brain irradiation therapy (XRT) was successfully replaced with additional intrathecal methotrexate for higher risk patients without lymphomatous features with fewer than 25% marrow blasts on day 7. Fewer CNS relapses, but more marrow relapses were encountered on the XRT arm compared with the intrathecal methotrexate arm. With longer follow-up, the outcomes are maintained as originally reported: 5-year EFS estimates from randomization are 73% ± 3% and 75% ± 3% for the XRT and intrathecal arms, respectively (Figure 7).

Infants treated with intensive therapy on CCG-1883 had a 4-year EFS of 39%, which represented a significant improvement compared with outcome on the earlier CCG-160 series of studies.²⁴ However, outcome is not significantly different for infants treated on CCG-1883 and the immediate predecessor study, CCG-107. Longer follow-up reveals an 8-year EFS of 37% for infants treated on CCG-1883.

Cytogenetic data from the CCG-1800 series were analyzed to identify specific abnormalities with prognostic significance. Outcomes were best (8-year EFS of 80%) for children with normal cytogenetics or high hyperdiploidy (modal chromo-

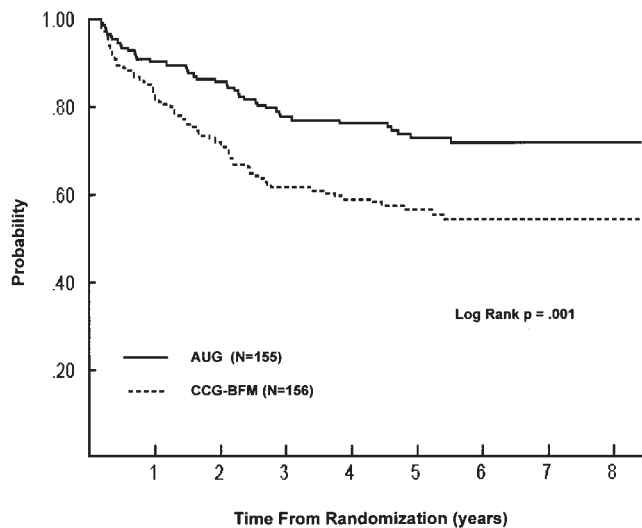


Figure 6 Outcome on the CCG-1882 trial (1989–1995) for higher risk ALL patients with a slow response to induction therapy. Probability of EFS from randomization for patients treated on the augmented regimen (AUG) or the CCG-modified BFM regimen (CCG-BFM).

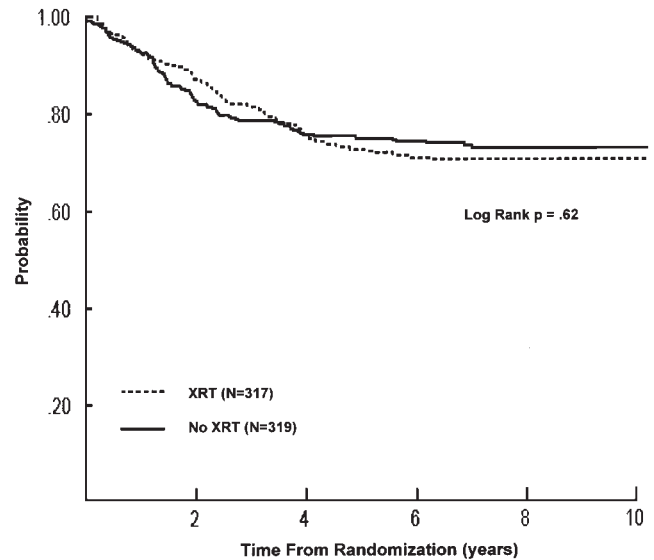


Figure 7 Outcome on the CCG-1882 trial (1989–1995) for higher risk ALL patients with a rapid response to induction therapy. Probability of EFS from randomization for patients treated with CCG-modified BFM with craniospinal irradiation (XRT) or CCG-modified BFM with intrathecal therapy only (no XRT).

some number >50; Table 3).^{37,38} We recently reported that patients with modal chromosome number <45 had very poor outcome,³⁸ and with additional follow-up, 5-year EFS for this subset is 35% (s.d. = 11%; Table 3). High hyperdiploid patients with modal chromosome number 54–58 had better outcome than those with modal number 51–53 or 59–68.³⁹ Also, within the high hyperdiploid subset, trisomies of chromosomes 10, 17, and 18 carried favorable univariate prognostic significance, trisomy 5 carried adverse prognostic significance, and trisomy of chromosome 4 had no prognostic significance.³⁹ Multivariate analysis found trisomy 10 the most important prognostic factor in the high hyperdiploid subset. Trisomy of chromosome 10 retained prognostic significance within both the standard risk ($P = 0.0002$; RR 0.40) and higher risk subsets ($P = 0.06$; RR 0.48). Outcome of patients with trisomies of both chromosomes 10 and 17 was superior to that of patients with trisomy of chromosome 10 alone.

As was previously reported,^{40–42} patients with a t(9;22)(q34;q11), as well as those with a balanced t(1;19)(q23;p13) had very poor outcome, with 5-year EFS of <45% (Table 3). The unbalanced der(19)t(1;19)(q23;p13), with a 5-year EFS of 76% (s.d. = 6%), was not an adverse risk factor. Patients with a t(4;11)(q21;q23), most of whom are infants, were found to have a 5-year EFS of <45%. Our previous observations^{43,44}

that infants with 11q23 abnormalities that did not involve chromosome band 4q21 had better outcome (5-year EFS = 57%, s.d. = 22%) than those with involvement of 4q21 (5-year EFS = 14%, SD = 6%) was maintained with longer follow-up. Moreover, non-infants with t(4;11) or other 11q23 abnormalities showed a similar pattern, with 5-year EFS of 50% (s.d. = 16%) and 68% (s.d. = 10%), respectively. Adverse outcome was also found for patients with abnormalities of 9p (6-year EFS of 61%).⁴⁵ Abnormalities of 12p⁴⁶ and 13q12–14⁴⁷ and deletions of chromosome band 6q⁴⁸ were not prognostic for the overall cohort. We also analyzed cytogenetic data among T-lineage ALL patients and found that most abnormalities lacked clear prognostic importance, although three of four patients with a t(8;14)(q24;q11) experienced an event.⁴⁹

Six hundred and forty-two children older than 1 year of age were screened by PCR for expression of the abnormal BCR-ABL, MLL-AF4, and E2A-PBX1 fusion transcripts resulting from the t(9;22)(q34;q11), t(4;11)(q21;q23), and t(1;19)(q23;p13) translocations.⁵⁰ Transcripts for BCR-ABL, MLL-AF4, and E2A -PBX1 were found in 2.3%, 0.7%, and 2.5% of cases, respectively. More than half of cases with fusion transcripts were ascertained among cases with missing or non-corresponding karyotypes. Among non-infant children with conventional cytogenetic data, the overall incidence rates for these translocations were 2.3%, 0.74%, and 3.5%, respectively.

These past trials have given rise to several 'reversals' in outcome where conventionally higher risk patients achieved a better outcome with successful experimental regimens than did conventionally lower risk patients with less aggressive, 'risk adjusted' therapies (Table 5). For example, intermediate risk patients treated with DI on CCG-105 had a better outcome than lower risk patients treated on CCG-104 and intermediate risk patients treated with double delayed intensification on CCG-1891 had a better outcome than lower risk patients treated with either a single or no DI on CCG-1881. Among higher risk patients, those younger than 10 years with $\geq 25\%$ marrow blasts on day 7 who received the augmented regimen had a better outcome than those younger than 10

years with $< 25\%$ marrow blasts on day 7 who received CCG-modified BFM regimen.

Discussion

In successive trials for childhood ALL conducted since 1978, the Children's Cancer Group (CCG) has obtained improvements in EFS for both NCI/Rome standard and higher risk and both B- and T-lineage patients.^{10,14–16,21,23,25,26,30,51,52} The day 7 and day 14 marrow response to therapy has been a consistent prognostic factor.^{53–55} Improved systemic therapy has allowed restriction of brain irradiation to fewer than 15% of patients. The cumulative incidence of second malignant neoplasm remains $< 2\%$.^{56,57}

Several lessons have emerged from this substantial experience:

- Initial response to therapy is an important predictor of outcome.
- Post-induction intensification improves outcome for both higher risk and standard risk patients. Intensive induction consolidation provided no additional benefit for standard risk patients who received DI. Augmented regimen 'rescues' higher risk patients with $> 25\%$ marrow blasts on day 7 response.
- Improved systemic therapy allows elimination of cranial irradiation for most patients.
- Substitution of dexamethasone for prednisone improves outcome for standard risk patients.

Early marrow response has been a consistent prognostic significance in both the CCG-100 and CCG-1800 series studies, and treatment stratification according to early response has allowed us to treat patients more effectively with $> 25\%$ blasts on day 7 of induction. The ALL BFM '90 trial had less success rescuing patients with a poor peripheral blood response to the prephase.⁵⁸ Reports by van Dongen *et al*,⁵⁹ Cave *et al*,⁶⁰ and Coustan-Smith *et al*,⁶¹ however, suggest that PCR-based and flow cytometry-based assays of minimal residual disease (MRD) may distinguish patients with favorable and unfavorable outcomes better than early marrow response. With PCR, approximately 50% of patients are MRD-negative at the end of induction and accumulate fewer than 20% of adverse events. With day 7 marrow evaluation, 50% of patients have $< 25\%$ marrow blasts, but still accumulate more than 40% of events. Given an overall 75% EFS, MRD would divide patients into subsets with EFS of 90% and 60% while day 7 response would divide patients into less divergent subsets with EFS of 80% and 70%. MRD may better divide patients into subgroups with differing clinical imperatives.

Post-induction intensification has been a successful strategy. Contrary to slogans like 'more is better'⁶² and invocations of the Goldie–Coldman hypothesis,⁶³ intensive induction-consolidation provided no added benefit for NCI/Rome standard risk patients who received DI. On the other hand, older patients with low WBC may benefit from intensive induction-consolidation. Thus, CCG has omitted the intensive induction-consolidation element of therapy for standard risk and has avoided 100 mg/m² of daunomycin, 2 g/m² of cyclophosphamide, and 10 hospital days per patient. CCG enrolls more than 600 standard risk patients per year and the savings exceed 6000 hospital days per year. This critical and unexpected finding focused our attention on post-induction intensification and led to subsequent randomized comparisons of single and double DI (CCG-1891) as well as further intensifi-

Table 5 Reversals of expected ordering of outcome for patient risk groups on CCG ALL trials

Greater risk	Lesser risk
CCG-105: Intermediate risk WBC $> 10\,000/\mu\text{l}$ and $< 50\,000/\mu\text{l}$ Age 1–9 years Delayed intensification 10-year EFS = 74%	CCG-104: lower risk WBC $< 10\,000/\mu\text{l}$ Age 1–9 years Standard 10-year EFS = 62%
CCG-1891: Intermediate risk WBC $\geq 10\,000/\mu\text{l}$ and $< 50\,000/\mu\text{l}$ Age 1–9 years Double delayed intensification 5-year EFS = 83%	CCG-1881: Lower risk WBC $< 10\,000/\mu\text{l}$ Age 1–9 years Standard 5 year EFS = 79%
CCG-1882: Higher risk WBC $\geq 50\,000/\mu\text{l}$ Age < 10 years Day 7 marrow blasts $\geq 25\%$ Augmented BFM 5-year EFS = 79%	CCG-1882: Higher risk WBC $\geq 50\,000/\mu\text{l}$ Age < 10 years Day 7 marrow blasts $< 25\%$ CCG-modified BFM ^a 5-year EFS = 76%

^aRegimen with XRT.

cation as used in the augmented regimen of CCG-1882. On the current CCG-1961 trial for higher risk ALL (1997–2001), which now includes the patients age ≥ 10 years with low WBC, all patients receive intensive induction-consolidation and we are examining the length and strength of post-induction intensification with a 2×2 design for patients with $< 5\%$ marrow blasts on day 7 of induction.

Simple changes in therapy may affect outcome. On CCG-1922, standard risk patients received 10 agents, namely, cytosine arabinoside, vincristine, prednisone, L-asparaginase, methotrexate, 6-mercaptopurine, 6-thioguanine, dexamethasone, Adriamycin, and cyclophosphamide. Despite the complexity of therapy, simple 'isotoxic' substitution of dexamethasone for prednisone in induction and maintenance increased EFS from 81% to 88%, even though all patients received dexamethasone during a single DI phase.²⁶ Perhaps other well-founded treatment modifications may also have a substantial clinical impact.

Patients with < 45 chromosomes,³⁸ a $t(9;22)(q34;q11)$,⁴⁰ and a balanced $t(1;19)(q23;p13)$,⁴² as well as infants with a $t(4;11)(q21;q23)$,^{43,44} who represented approximately 6% of all patients, had strikingly adverse outcome. Patients with normal or high hyperdiploid karyotypes had about a 40% reduction in risk of treatment failure. However, a substantial percentage of all treatment failures, 40%, occur among patients with favorable normal or hyperdiploid karyotypes and present a continuing opportunity for better treatment.

Our data and those of others suggest that single cytogenetic/molecular findings fail to define homogeneous populations. Standard risk patients with trisomy of chromosome 10 appear to have better outcome than higher risk patients with trisomy of chromosome 10 (8-year EFS of 87% vs 81%).⁶⁴ Infants with $t(4;11)$ have an inferior outcome compared to children with $t(4;11)$.^{44,65,66} On BFM studies, patients with $t(9;22)(q34;q11)$ or $t(4;11)(q21;q23)$ and a good 'prednisone' response have a better outcome than patients with the same translocation and a poor prednisone response.^{67,68} Micro-array technology^{69,70} may help us move to a multi-marker classification scheme to match the complex heterogeneity of childhood ALL.

Successful CCG trials have given rise to several 'reversals' in outcomes where conventionally higher risk subsets achieved a better outcome with successful experimental regimens than did conventionally lower risk patients with less aggressive, "risk adjusted" therapies. The fact that a population achieves a good outcome with good therapy does not negate the possibility that a yet better outcome might be obtained with yet better therapy. On the other hand, otherwise helpful treatment elements may prove redundant in a favorable subset. Conversely, resistant subsets – like infants and Ph^+ ALL – may show no benefit from generally helpful treatment elements.

Parmar *et al*⁷¹ observed that many, if not most of new anticancer treatments tested in NCI or British Medical Research Council-sponsored trials are ineffective or at best, marginally effective. CCG experience in ALL has been better than this somber observation. Over the past 15 years, CCG has shown a clinically significant advantage for an experimental regimen in a majority of randomized trials. Three possible reasons for our relative success deserve consideration. First, childhood ALL is a chemosensitive malignancy. Patients in relapse still usually respond to therapy similar to that used initially and thoughtful modifications of primary chemotherapy might be expected to have a better than 'average' chance for benefit. However, a fair number of other reason-

able modifications of conventional ALL therapy have failed to show benefit.

Second, we conducted trials with adequate sample size to detect moderate treatment differences on the order of a 25–30% reduction in hazard. Gains in ALL, as elsewhere, have generally been of only moderate magnitude. A 5% point gain in ALL benefits as many children as a 25% gain in AML or 15% gain in neuroblastoma.⁷² Adequate sample size assures that we identify useful interventions that boost EFS and serve to direct future efforts. Recognition of numerous cytogenetic/molecular subsets and the importance of initial response to therapy raise the intriguing question whether specific treatment elements might benefit specific subsets. Useful examination of treatment effects within cytogenetic/molecular genetic/response subsets will require better ascertainment and enormous trials. Studies of agents like STI571,^{73,74} which are targeted for small patient subsets may require international collaborations.

Third, we identified a successful strategy and pursued it. Effective post-induction intensification, based on work by Riehm and the BFM group, was tested rigorously between 1983 and 1988 and pursued relentlessly thereafter. This breakthrough idea made subsequent gains possible. Clinical and laboratory observations linking treatment outcome to glucocorticoid steroid sensitivity^{75,76} and our demonstration of the superiority of dexamethasone over prednisone²⁶ may provide additional opportunities. Further opportunities may derive from our observation that patients with a suboptimal response may be rescued with changes in therapy 6 weeks later.¹⁶ More precise assessment of response might facilitate more appropriate treatment allocation.

The ALL trials described herein show reductions in failure rate between 26% and 44%. For the future, integration of insights from clinical trials, studies of the biology of leukemic blasts, and studies of host pharmacology may lead to further progress.

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