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## DIFFERENCES IN PROGNOSIS FOR BOYS AND GIRLS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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**Summary** In the period 1968–78, 3161 children were enrolled in six studies of acute lymphoblastic leukaemia by participating institutions of the Childrens Cancer Study Group. In the first two studies, which did not include central-nervous-system (CNS) prophylaxis in the treatment programme, the outcome for male and female patients was very similar. In the following four studies, which included radiation prophylaxis to the

CNS, a difference in outcome favouring females appeared consistently. This difference began about 6–12 months after initial remission and was further accentuated by withdrawal of therapy. Some of these studies also included a randomised trial of duration of therapy, studying 3 versus 5 years of maintenance treatment. Analysis of these studies suggests that sex group has implications both for duration of treatment and for optimum central-nervous-system prophylaxis.

### Introduction

A NUMBER of reports on the treatment of children with acute lymphoblastic leukaemia have identified certain patient characteristics as having a major influence on disease outcome.<sup>1-7</sup> Initial white-blood-cell count and age at diagnosis have been shown to be important determinants of outcome. Reports on some of the other characteristics have been conflicting. One such factor is the patient's sex. Some reports indicate a generally better outcome for females,<sup>8-11</sup> whereas other studies have shown no significant difference in prognosis.<sup>2,6,12</sup> There are also reports of prognostic differences favouring females in selected patient subgroups<sup>7</sup> and after long remissions or the discontinuation of therapy.<sup>13-15</sup> To study this issue, we examined data from a large series of patients treated on leukaemia trials of the Childrens Cancer Study Group (CCSG), a multi-institution network of hospitals treating children with cancer.

### Patients and Methods

In the period 1968–78 the CCSG enrolled patients on six large randomised trials of therapy for children (defined in most of these studies as less than 16 years of age at diagnosis) with acute lymphoblastic leukaemia. 3161 patients were treated (table 1). The first two studies (CCG-803, CCG-903) did not have central-nervous-system (CNS) prophylaxis as part of the treatment programmes. The third and fourth trials (CCG-101, CCG-143) were designed to study the efficacy of various modes of CNS prophylaxis: CNS irradiation was used in five of the six regimens and intrathecal methotrexate in one. In the fifth and sixth studies (CCG-141, CCG-141A) radiation prophylaxis was given to all the patients in a standard treatment approach. In studies 3, 4, and 5 patients who achieved a long continuous remission were randomised for duration of treatment (3 versus 5 years). The entire treatment programme for studies 1–6 have been reported in detail elsewhere.<sup>10,16-19</sup>

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TABLE I—CHILDREN'S CANCER STUDY GROUP ACUTE LYMPHOBLASTIC LEUKAEMIA STUDIES

Study	Date	No. of patients	CNS prophylaxis
1. CCG-803	1968-70	422	} No
2. CCG-903	1970-72	499	
3. CCG-101	1972-74	724	
4. CCG-143	1974-75	212	} Yes
5. CCG-141	1975-77	895	
6. CCG-141A	1977-78	409	

Statistical analysis of the data from these studies used standard life-table statistics<sup>20,21</sup> for comparisons of remission and survival results, and basic contingency table methods for tests of proportions<sup>22</sup> in assessing induction outcome. Estimates of the relative event rate were calculated with a life-table method.<sup>21</sup>

In several of the following life-table results, haematological remission duration has been used as the index of comparison, since marrow relapse is the most severe type of recurrence and survival following a marrow relapse is usually very short. When comparisons using other outcome indices (e.g., continuous complete remission, CNS remission, survival) would yield different conclusions, those results are indicated.

### Results

In this series of studies the success in achieving an initial remission was nearly identical for males and females for each specific induction treatment programme (table II), although there was a gradual overall improvement in the studies as the induction therapy was changed. Thus, there is no indication of a sex difference for achievement of an initial remission.

In study 1, in which no CNS prophylaxis was given, the duration of continuous complete remission (i.e., absence of relapse in marrow, CNS, and other extra-medullary sites) was essentially the same for males and females. Fig. 1 shows the life-table comparison of haematological remission for males and females ( $p=0.39$ ), illustrating the same basic outcome for the two sexes. Also, the survival results in that study were nearly identical for males and females.

In study 2 also, CNS prophylaxis was not given. Haematological remission was similar for males and females. Survival results were better for females, but this difference appeared very late and seems to have been related to a better outcome for females after discontinuation of therapy.

Study 3 was designed specifically to study the effectiveness of various approaches to CNS prophylaxis, and all patients were given the same induction and maintenance chemotherapy. There were four basic treatment regimens to which patients were randomised after a successful remission induction. One regimen gave 2400 R of radiation to the cranium and the spine plus 1200 R to other possible disease sanctuary sites (gonads, kidneys, spleen, liver, thymus). Another regimen gave 2400 R to the cranium and spine only. A third regimen gave 2400 R to the cranium plus a course of

TABLE II—REMISSION-INDUCTION RATES

Study	Treatment	Remission-induction rate (%)	
		Males	Females
1. CCG-803	Prednisone, methotrexate	77.7	78.0
2. CCG-903			
3. CCG-101	Vincristine, prednisone	90.1	89.8
4. CCG-143			
5. CCG-141	Vincristine, prednisone, L-asparaginase	93.0	92.9
6. CCG-141A			

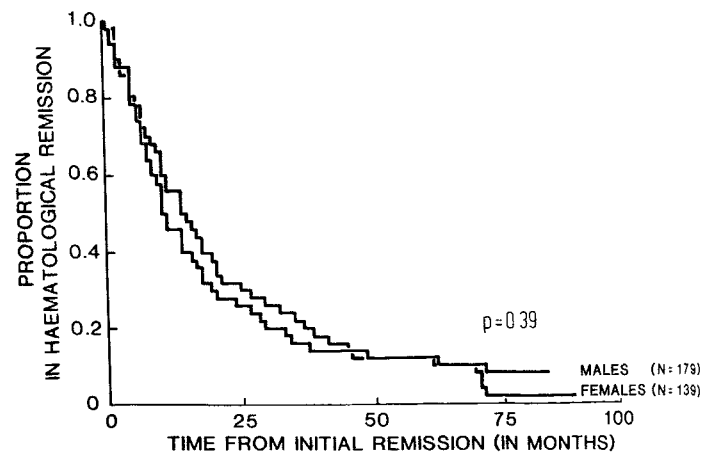


Fig. 1—Study 1 (CCG-803): haematological remission by sex group.

six doses of intrathecal methotrexate (IT MTX) over a 3-week period. The fourth regimen gave only the six doses of IT MTX. A few months after the study was closed to patient entry a very high rate of initial relapse in the CNS was apparent in patients given IT MTX as the only CNS prophylaxis. At that time it was recommended that all patients still in a continuous complete remission on that regimen be recalled for radiation prophylaxis to the CNS. About 90% of the patients eligible for recall received late radiation prophylaxis to the CNS.

For the study population who achieved a remission and were randomised in study 3, there is a highly significant difference by sex group for continuous complete remission, haematological remission, CNS remission, and survival. Fig. 2 shows the difference in haematological remission favouring girls ( $p < 0.001$ ). The life-table estimate of the relative event rate indicates a 1.7-fold higher rate of marrow relapse in boys. Although this was the general result in the study, substantial differences in outcome between and within sex groups were seen with the different treatment regimens.

Study 4 also was designed to study CNS prophylaxis with the same induction and maintenance therapy used in study 3. The patients who achieved remission in study 4 were randomised to one of two radiation-prophylaxis treatments to the CNS. The first regimen gave cranial-spinal irradiation at 1800 R, and the second gave only cranial irradiation at 1800 R plus six doses of IT MTX. Thus, this study represented a randomised trial of two of the CNS regimens from study 3, but with the radiation given at a lower total dose.

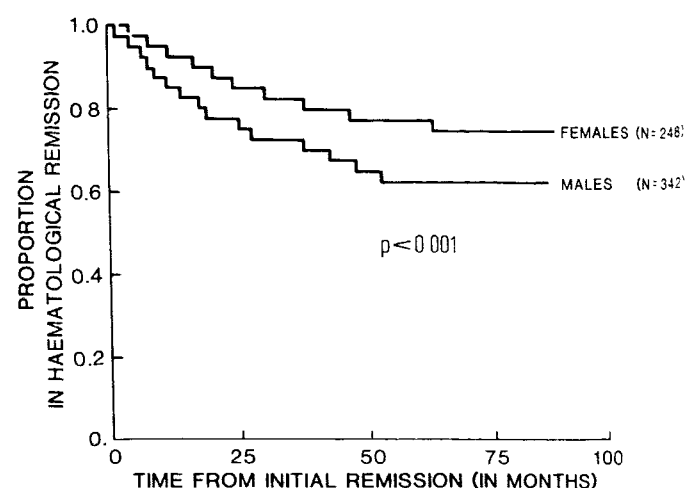


Fig. 2—Study 3 (CCG-101): haematological remission by sex group.

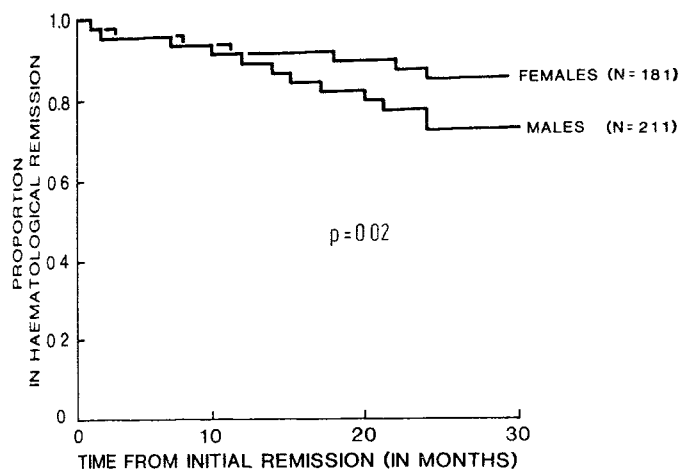


Fig. 3—Study 6 (CCG-141A): haematological remission by sex group.

Comparisons of outcome by sex group in study 4 again showed a clear difference favouring females. For example, the relative haematological relapse rate for males was 1.7 times greater than that for females, as it was in study 3. In study 3 the beginning of the difference in outcome for males and females appeared quite early, at about 3 months from remission, and in study 4 this difference began to appear at about 6 months from remission.

Studies 5 and 6 were randomised studies examining different approaches to treatment in induction and maintenance, all patients receiving the same CNS prophylaxis of 2400 R cranial irradiation plus the short course of IT MTX. In both of these studies a difference in outcome favouring females is evident. For study 5 the difference began about 18 months from initial remission. The relative marrow relapse rate was 1.3 times higher in males than females, and the life-table comparison was significant ( $p=0.03$ ). In study 6 the difference began 12 months from initial remission (fig. 3) and was somewhat greater than that in study 5, with a 1.7-fold higher relapse rate for males than females.

Table III summarises the haematological remission results for all six studies at 36 and 60 months from initial remission. Among the patients in study 3 who received some type of radiation prophylaxis, females fared better than males; among those who received only the short course of intrathecal chemotherapy as prophylaxis, the outcome was about the same for the two sexes. Thus the use of extensive CNS prophylaxis, such as radiation therapy, seems to provide a greater differential benefit for female patients than males.

To examine studies 3 and 4 in more detail, it is useful to consider the results for continuous complete remission within subgroups determined by the level of the initial white-blood-cell count (WBC),  $<20\,000/\mu\text{l}$  and  $>20\,000\ \mu\text{l}$ . Table IV gives the data for the low-WBC patients within sex group.

TABLE III—HAEMATOLOGICAL-REMISSION (HR) PROPORTIONS

Study	HR at 36 mo		HR at 60 mo	
	Males	Females	Males	Females
CCG-803	0.16	0.21	0.11	0.11
CCG-903	0.25	0.31	0.15	0.21
CCG-101 (IT MTX)	0.76	0.75	0.65	0.69
CCG-101 (XRT)	0.69	0.84	0.62	0.80
CCG-143	0.72	0.84	0.65	0.79
CCG-141	0.68	0.75	0.61	0.72
CCG-141A	0.68	0.80	..	..

XRT=radiation therapy.

TABLE IV—CCG-101,-143: LOW-WBC\* CHILDREN IN CONTINUOUS COMPLETE REMISSION AT 36 MO

Study	CNS prophylaxis	No. of patients		Estimated percentage in remission	
		Males	Females	Males	Females
CCG-101	C/S 2400R + EF	50	44	69	77
	C/S 2400R	60	46	75	86
	C 2400R + IT MTX	65	53	68	81
	IT MTX	57	48	61	58
CCG-143	C/S 1800R	36	28	75	73
	C1800R + IT MTX	33	22	74	82

\*WBC at diagnosis  $<20\,000/\mu\text{l}$  C/S=cranial-spinal irradiation. EF=extended-field irradiation. C=cranial irradiation.

For both male and female patients, the IT MTX regimen has a result which is somewhat inferior to that of the radiation regimens. This difference is predominantly due to an excess of CNS relapses with the IT MTX regimen. In the male patients, however, the survival results are currently as good for that regimen as for other treatments. In the female patients the survival is marginally poorer. The reason that survival on this regimen for both males and females is roughly comparable to that on the other regimens is that a number of patients in this WBC group who had an initial CNS relapse were successfully retreated and continue in a long subsequent remission.

In the high-WBC patients (table V) the results are much more striking. In study 3 males receiving cranial irradiation plus the short course of IT MTX did best, with approximately 30% more patients in continuous complete remission at 3 years than with the other regimens, all of which had about the same outcome. Study 4 partially confirms this result at the lower radiation dose, the regimen of cranial irradiation plus IT MTX having 32% more patients in remission at 3 years than the cranial-spinal irradiation regimen.

In females with high WBC a different pattern is seen. In study 3 the more extensive the CNS irradiation prophylaxis, the better the outcome. Females receiving cranial-spinal irradiation with or without extended-field radiation have had an excellent outcome, with 80% and 69%, respectively, in continuous complete remission at 36 months. The cranial irradiation plus IT MTX group had only 46% in continuous complete remission at that time, whereas the females assigned to the IT MTX regimen had just 14%. In study 4 the cranial irradiation plus IT MTX regimen had a marginally better outcome than the cranial-spinal regimen.

An important question in the treatment of childhood acute lymphoblastic leukaemia concerns the duration of therapy. A large number of patients from some of these CCSG studies

TABLE V—CCG-101,-143. HIGH-WBC\* CHILDREN IN CONTINUOUS COMPLETE REMISSION AT 36 MO

Study	CNS prophylaxis	No. of patients		Estimated percentage in remission	
		Males	Females	Males	Females
CCG-101	C/S 2400R + EF	26	15	32	80
	C/S 2400R	30	16	33	69
	C 2400R + IT MTX	30	11	60	46
	IT MTX	24	15	29	14
CCG-143	C/S 1800R	9	13	22	77
	C1800R + IT MTX	13	13	54	85

\*WBC at diagnosis  $<20\,000/\mu\text{l}$  C/S=cranial-spinal irradiation. EF=extended-field irradiation. C=cranial irradiation.

have been entered onto randomised trials of therapy duration. Patients from studies 3 and 4 who maintained a continuous complete remission for 3 years and who agreed to randomisation were assigned either to stop treatment at that time or to continue maintenance therapy for a further 2 years. Patients in study 5 who maintained a 3-year continuous complete remission and agreed to randomisation were randomised to one of three regimens: (1) stop treatment, (2) receive induction-type therapy for a 28-day consolidation period and then stop treatment, or (3) continue treatment for 2 more years. In study 5 all male patients, to be eligible for randomisation, were required to have a bilateral open-wedge testicular biopsy negative for leukaemic infiltrates. The first duration-of-therapy study has had 317 patients randomised to the two regimens with a median follow-up of 36 months (range 20–55 months) after randomisation. 82% of the patients assigned to the 5-year duration-of-therapy study have completed their therapy. The second duration-of-therapy study has had 248 patients randomised with a current median follow-up of 9 months (range 0–23 months) since randomisation. The first duration-of-therapy study indicates clearly the higher incidence of late leukaemic recurrence among males achieving a long continuous complete remission (table VI). Males have had a substantial excess of recurrence

TABLE VI—RANDOMISED DURATION-OF-THERAPY STUDY\* FIRST OCCURRENCE OF DISEASE OR DEATH AFTER 3 YEARS IN CONTINUOUS COMPLETE REMISSION

Treatment group	No. randomised	Bone-marrow relapse	CNS relapse	Testicular relapse	Death in remission
Males: therapy continued	86	4	5	5†	0
Males: therapy discontinued	87	12	0	10	0
Females: therapy continued	71	2	2	..	3
Females: therapy discontinued	73	6	2	..	0

\*Patients from studies 3 and 4 (CCG-101 and CCG-143).

†2 patients had their testicular relapse after completing therapy at 5 years.

on both the continue-therapy and discontinue-therapy regimens (14 males versus 4 females and 22 versus 8, respectively). For females the current total of first events is nearly the same for both the continue and discontinue treatment regimens. In addition, three of the seven events on continued therapy have been deaths in remission. Since risk of relapse is increased for a period after discontinuation of treatment, these data raise the possibility that after therapy has been completed for all patients, female patients assigned to the longer duration of therapy (5 years) could fare somewhat worse than those treated for only 3 years. These results suggest that duration of treatment in excess of 3 years for females maintaining a continuous complete remission may be unnecessary, and studies of even shorter duration of treatment are warranted. A randomised duration-of-therapy study in Great Britain involving substantially fewer patients suggested that treatment for 2 years was as beneficial for females as treatment for 3 years.<sup>23</sup>

Our results for male patients still show an excess of relapses in the group discontinuing treatment at 3 years. However, 2 patients have relapsed shortly after stopping treatment at 5 years and more such relapses may happen after additional patients on that regimen have their treatment stopped. Thus, until all male patients originally assigned to continue

treatment reach the 5-year point, discontinue therapy, and have adequate follow-up after stopping, we shall not know whether males have benefited from more than 3 years of treatment. Of interest in this regard is the British study which, after showing an early transient benefit to males given 3 years' treatment instead of 2 years, ultimately resulted in exactly the same outcome for males irrespective of the treatment duration.<sup>23</sup>

The results of the second duration-of-therapy study (study 5), though preliminary, are of definite interest in regard to duration of treatment for males. The early results show an incidence of occult testicular involvement of approximately 9% (23/254), as detected by routine testicular biopsy in male patients reaching 3 years of continuous complete remission. Since these patients were not eligible for randomisation, a somewhat different population of male patients was studied than in the previous duration-of-therapy study in which biopsies were not required. The early results from the second study show identical numbers of recurrences for the two early discontinuation regimens and the continue-therapy regimen. This is unlike the early results in the first duration-of-therapy study, in which a substantial number of testicular relapses was the main cause of the poorer outcome of the discontinue-therapy group. Also, the second study is not showing at present any important difference in outcome between males and females. At present, only 2 male patients of 231 with negative testicular biopsies at 3 years have subsequently had an isolated first relapse in the testes. There are also 2 patients who had concurrent marrow and testicular recurrence as a first relapse following a negative testicular biopsy. Thus, it is possible that testicular biopsy can identify a large percentage of the males who will require no more than 3 years of treatment. Further follow-up on this study will be necessary to clarify the issue.

### Discussion

This large series of over 3000 children with acute lymphoblastic leukaemia treated on recent CCG protocols was retrospectively studied for differences in outcome for males and females. In each of the six studies, males and females had equal success in achieving an initial remission. In the first two studies of the series no CNS prophylaxis was given, and the duration of remission was similar for the two sexes. In the last four studies CNS prophylaxis was given routinely, and each study has shown a striking difference in remission duration favouring females. One treatment regimen in study 3 gave only a very short course of IT MTX as initial CNS prophylaxis, whereas all other regimens included radiation prophylaxis. Almost all patients on the IT MTX regimen who were still in a continuous complete remission after the study was closed to entry were subsequently given late radiation prophylaxis to the CNS. As with study 1 and study 2, this treatment regimen did not show any difference in ultimate disease outcome for males and females, although all the other radiation regimens in this study showed a better outcome for females. These results suggest that the introduction of extensive CNS prophylaxis (i.e., radiation therapy at an adequate total dose) and the delivery of this therapy early in the course of treatment provided a greater benefit to females. Another report showing females to have a better outcome than males also suggests that modern therapy may have been a factor in the emergence of this difference in prognosis.<sup>8</sup>

Although there was variation in results in the studies, the difference in outcome first begins to appear about 6–12

months after initial remission. This difference in outcome increases further after discontinuation of treatment. This latter result has been noted by others<sup>13-15,24</sup> and is accounted for in large part by the occurrence of testicular relapse in a proportion of males who have stopped therapy.

Whereas the studies with CNS prophylaxis indicate that females have a better remission experience than males, the two randomised studies which examined alternative forms of CNS prophylaxis show some interesting variations in outcome dependent on treatment regimen, initial WBC, and sex. It is possible that less aggressive CNS treatment strategies than those often used (e.g., lower total doses of 1800 R or less, and/or prolonged intrathecal chemotherapy) would control the disease adequately in both male and female patients with low WBC at diagnosis and would represent less potential risk for long-term effects of therapy in this low-risk group. In high-WBC male patients both studies showed that cranial irradiation plus a short course of IT MTX was superior to cranial-spinal irradiation and also suggested that the former given at 1800 R may be sufficient treatment. For high-WBC females the studies were not entirely consistent, although in one study the outcome was better with more treatment to the CNS and other sanctuary sites. The other study suggested a very good outcome for this group of females with the 1800 R dose of radiation on either the cranial plus IT MTX or the cranial-spinal radiation regimens. The data from these two studies indicate that the optimum CNS prophylaxis for a patient may be related to both the patient's sex and initial WBC.

The randomised duration-of-therapy studies that enrolled patients from studies 3 and 4 show substantial differences in late outcome, favouring females. These data and the results from study 5 indicate that females generally require no more than 3 years of treatment. For males it is not yet clear whether only 3 years of treatment is an adequate strategy for all males reaching that point in a continuous complete remission. Early results from the second duration-of-therapy study suggest the importance of using testicular biopsy to screen out males who would be at high risk of relapse once therapy is stopped. If the present trends continue, this screening procedure may provide a good technique to identify a large proportion of the males who also require no more than three years of treatment. Further randomised studies of shorter treatment duration are certainly warranted. The CCSG is now beginning a study of 2 versus 3 years of treatment for both male and female patients, males being required to have a negative testicular biopsy to be eligible for randomisation.

Although, clearly, there are important differences in outcome between male and female patients, the underlying biological reasons are not fully understood. Evans et al. have suggested that differences in the distribution of such prognostic factors as age at diagnosis and initial WBC may account for differences in outcome.<sup>12</sup> This is true to a slight degree in our studies, but adjustment for these factors still leaves a major difference in outcome to be explained. T-cell disease is much more common in males than females,<sup>25-27</sup> and although the six studies reported here did not have determination of cell-surface markers as an entry requirement, the early results of some current CCSG studies are indicating that marker status may explain some of the sex difference in prognosis. Most of the early difference in male/female outcome for this recent series can be explained by the higher frequency of T-cell disease in males and the greater relapse rate for that subtype. Further follow-up will be necessary to determine if that factor will also explain

differences in outcome that occur late (e.g., after stopping therapy). Since mediastinal mass is known to have a strong correlation with the presence of T-cell disease, we investigated studies 3 to 6 in the present report to see whether mediastinal-mass status explained a large part of the prognostic difference for males and females. Those analyses showed that mass status accounted for a negligible part of the prognostic difference. Therefore, factors other than immunological cell-marker category and other commonly studied prognostic variables will require investigation to explain more adequately the reasons for this difference in outcome.

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