Prognostic importance of myelosuppression during maintenance treatment of lymphoblastic leukaemia

G DOLAN,* J S LILLEYMAN,* AND S M RICHARDS†

● *On behalf of the Leukaemia in Childhood Working Party of the Medical Research Council*

**Department of Haematology, The Children's Hospital, Sheffield and †Clinical Trial Service Unit, Radcliffe Infirmary, Oxford*

SUMMARY Children from the UKALL V trial were studied to assess the clinical importance of myelosuppression during uninterrupted 'maintenance' treatment of 'standard risk' lymphoblastic leukaemia. Those receiving daily 6-mercaptopurine and weekly methotrexate who were in first remission 20 months from diagnosis were divided into two groups on the basis of whether or not they had ever had an absolute neutrophil count of $<0.5 \times 10^9/l$ recorded during maintenance treatment up to that time. Of 105 evaluable children, 45 (43%) became neutropenic at least once, and 60 (57%) did not. Seven (16%) of the neutropenic group subsequently relapsed compared with 27 (45%) of the remainder. This difference was still significant if the analysis was stratified by total treatment time (two or three years), age, sex, or diagnostic white cell count. Seven (16%) neutropenic children died in remission, compared with one (2%) of the non-neutropenic children.

Therapeutic myelosuppression during standard maintenance treatment of 'standard risk' lymphoblastic leukaemia is associated with increased toxicity but a reduced risk of relapse. The unexplained improvement in long term survival in the United Kingdom in recent years may in large part be due to this.

Current conventional treatment of other than 'high risk' childhood lymphoblastic leukaemia includes a long phase of continuing 'maintenance' chemotherapy. This usually consists of daily 6-mercaptopurine and weekly oral methotrexate, together with occasional pulses of vincristine and prednisolone.

How important this phase of treatment is may depend on the nature and intensity of remission induction, consolidation and/or intensive 'blocks' of chemotherapy given in addition. From the observed incidence of relapse in early trials without prolonged maintenance,¹ however, and in patients who default from follow up, there can be little doubt that for many children on various regimens it is important.

Further evidence is available from UKALL V, a recent United Kingdom Medical Research Council (MRC) trial which compared three different ways of giving the same cumulative dose of 6-mercaptopurine and methotrexate in maintenance. The results were not the same, and giving 6-mercaptopurine continuously appeared to be associated with more effective disease control than intermittent dosing.² The basic design of a succeeding MRC trial, UKALL VIII, did not appear to differ substantially from the UKALL V 'continuous' arm, but none the less produced a sustained and striking improvement in long term disease free survival, which has yet to be explained.³

An impression gained by clinicians involved in UKALL VIII was of a greater incidence of treatment induced myelosuppression and morbidity during maintenance. This appeared to be due to higher cumulative doses of 6-mercaptopurine and methotrexate being given as a result of more rigidly defined prescribing criteria than in previous trials.

● Members of the Working Party during UKALL V: R M Hardisty (chairman), C C Bailey, P R H Barbor, N D Barnes, A W Craft, J M Chessells, S I Dempsey, O B Eden, P M Emerson, D I K Evans, J J Fennelly, D A G Galton, N Harker, F G H Hill, H E M Kay, D N Lawson, J S Lilleyman, T J McElwain, J R Mann, J Martin, P H Morris-Jones, M G Mott, J Peto, M Radford, M R Sandland, E N Thompson, M L N Willoughby.

If more children on UKALL VIII became neutropenic and more survived their disease, it seemed obvious to ask if the two phenomena could be related. To answer this question we chose to examine the 'continuous' arm of UKALL V. The design was very similar to UKALL VIII, but we anticipated there would be a larger proportion of patients who did not become neutropenic giving more equal group sizes for analysis. This report describes our findings.

Patients and methods

All children in the United Kingdom with 'standard risk' lymphoblastic leukaemia between the ages of 1 and 14 years, who had no meningeal disease or mediastinal mass, and who had a diagnostic white cell count $<20 \times 10^9/l$ were eligible for UKALL V. The regimen has been described in detail elsewhere,² but briefly consisted of remission induction with four doses of vincristine, four weeks of prednisolone, and four doses of L-asparaginase ($10\,000\text{ U/m}^2$) after marrow recovery. This was followed by cranial irradiation, five doses of intrathecal methotrexate, daily 6-mercaptopurine (50 mg/m^2), and two further weeks of vincristine and steroid treatment before all patients were randomised to one of three continuing (maintenance) regimens. The 'continuous' arm consisted of 12 week cycles with a pulse of vincristine and steroids every six weeks, weekly oral methotrexate (20 mg/m^2), and daily 6-mercaptopurine with a target dose of $50\text{--}70\text{ mg/m}^2$. The duration of treatment was randomly allocated to two or three years. Co-trimoxazole was not given as part of the protocol.

The trial opened in January 1976 and closed in March 1979, accruing 528 patients. The record cards for all children who remitted, who did not relapse before the completion of six cycles (18 months) of maintenance treatment, and who received the 'continuous' arm were reviewed. Every recorded neutrophil count from the start of randomised treatment was extracted and entered into a computer file containing other patient details including treatment outcome.

Patients were divided into two groups simply on the basis of whether they had ever had a recorded neutrophil count below $0.5 \times 10^9/l$ or not. The two groups so defined were compared for any difference in treatment related mortality and recurrence of disease using the log rank method with two tailed p values, and simple $2 \times 2\ \chi^2$ tests with Yates's correction.

Results

Four hundred and ninety six patients remitted on

UKALL V, of whom 161 were allocated to the 'continuous' arm of treatment. One hundred and five completed their first six cycles of treatment every three months in remission and had their neutrophil counts examined. They form the basis of the present study.

Of the 105, 60 (57%) never produced a neutrophil count below $0.5 \times 10^9/l$ whereas 45 (43%) did so on at least one occasion. With a minimum follow up time of eight and a half years, seven (16%) of the neutropenic children have relapsed compared with 27 (45%) of the others (see figure). This difference is significant ($2 \times p=0.002$; log rank), and remains so if the duration of remission is stratified by age (<3 , $3\text{--}8$, >8 years: $2 \times p=0.004$), diagnostic white cell count (<10 , $>10 \times 10^9/l$: $2 \times p=0.002$), sex ($2 \times p=0.003$), or all three ($2 \times p=0.05$). In the 'continuous' arm of UKALL V there was a significant excess of marrow relapses in those randomised to two years rather than three years treatment ($p=0.02$, as described elsewhere²), but even if the neutropenic and non-neutropenic groups are stratified for this variable, the difference in relapse rate remains significant ($2 \times p=0.02$). The proportions of the two groups in the age, sex, white cell count, and treatment categories is shown in the table.

Of the 105, eight (8%) died in remission: seven from the neutropenic group (16%) and one of the others (2%). The excess of remission deaths in the neutropenic group is significant ($\chi^2=5.2$; $p<0.05$). The treatment related mortality pattern makes the difference in eight year event free survival (as opposed to remission duration) between the neutropenic (69%) and non-neutropenic (53%) groups no longer significant ($2 \times p=0.11$), though the trend remains.

Figure Duration of remission for 105 children on UKALL V 'continuous'. Time scale in years from diagnosis; (---) 45 who had a neutrophil count $<0.5 \times 10^9/l$ during the first 18 months of maintenance treatment on at least one occasion; (—) 60 who never had a neutrophil count $<0.5 \times 10^9/l$ during the same period. Log rank: $2 \times p=0.002$.

Table UKALL V 'continuous' regimen

Neutrophil count during weeks 11-96	Total	Boys	Girls	Diagnostic white cell count		Age (years)			Treatment (years)*	
				$>10 \times 10^9/l$	$<10 \times 10^9/l$	<3	3-8	8+	2	3
Patients who had count $<0.5 \times 10^9/l$:										
At least once	45	18	27	11	34	12	29	4	18	17
Never	60	31	29	13	47	9	41	10	20	24
Total	105	49	56	24	81	21	70	14	38	41

*Several of the 105 patients relapsed before this randomisation occurred.

The timing of neutropenia did not seem important in terms of whether it occurred within the first nine months of treatment or later, nor did the frequency of neutropenic episodes in terms of the number of recorded neutrophil counts $<0.5 \times 10^9/l$ provided it was less than three. Children who had profound neutropenia on more than four occasions (there were only four so the numbers are very small) may paradoxically have a higher relapse rate. Two relapsed, and comparison with those who became neutropenic one, two, or three times gives $2 \times p=0.01$; the observed:expected ratio was 2.7.

The method of defining neutropenia did seem important, and no difference in the relapse rate of the 105 could be seen if the patients were divided around a threshold neutrophil count of $1.0 \times 10^9/l$, or if a median value for each patient was calculated.

Discussion

The clear implication from this cohort study is that treatment induced myelosuppression during continuing (maintenance) therapy for standard risk lymphoblastic leukaemia is associated with greater toxicity but better disease control. Most of the episodes of neutropenia observed would have been due to chemotherapy as another major myelosuppressant, co-trimoxazole, was not used in UKALL V.

The findings support the hypothesis that much of the improvement in long term survival seen in the United Kingdom after 1980 is due to increased cytotoxicity of 6-mercaptopurine and methotrexate maintenance treatment. Before that time, although the protocol design and doses were similar, clinicians had no guidelines on dose adjustment in the face of neutropenia or thrombocytopenia and many tended to use amounts which avoided profoundly low counts, as can be seen from the high proportion of children (57%) in our study cohort who never had a neutrophil count below $0.5 \times 10^9/l$ during the first 18 months treatment. The incidence of neutropenia

in UKALL VIII is still being analysed, but it would appear to be higher.

Surprisingly few studies have looked at this aspect of maintenance chemotherapy before, though 18 years ago Pinkel *et al* showed that halving the drug doses shortened remission and reduced long term survival rates.⁴ Van Eys *et al*, for the Pediatric Oncology Group, prospectively studied 430 children with good risk lymphoblastic leukaemia who were randomly assigned to continuing treatment designed to maintain a total white cell count of either (a) $1.5-3.0$ or (b) $3.0-5.0 \times 10^9/l$ and found no difference in disease free survival, though the children in group (a) appeared to suffer more serious infections.⁵ Superficially this would appear to contradict our findings, but two points should be stressed about the Pediatric Oncology Group study. Firstly, the overall results, like UKALL V, were not good for either (a) or (b) by current standards (five year disease free survival of $<50\%$ for good risk lymphoblastic leukaemia) and secondly, part of the protocol for both groups was to keep the neutrophil count well above $0.5 \times 10^9/l$. It is possible that patients in both arms of the study from the Pediatric Oncology Group received inadvertent inadequate treatment in much the same way as the non-neutropenic patients in UKALL V. More recently Schmiegelow *et al* found that the mean white cell count during maintenance treatment was a prognostic factor second only in importance to the diagnostic white cell count in a group of 84 Nordic children.⁶ Despite different methods of analysis (the mean white cell count and minimum neutrophil count measure different things) their patients were similar and the Scandinavian findings and conclusions broadly agree with our own.

The practical point is that 'classical' maintenance treatment can probably be made more effective in terms of disease control if the doses of 6-mercaptopurine and methotrexate are pushed to the point where occasional neutrophil counts $<0.5 \times 10^9/l$ are produced. This has been standard practice for years

in some centres,⁷ but is by no means always the case. In many patients it may have been achieved fortuitously in UKALL VIII, and this would explain the improved results. The greater treatment induced morbidity and mortality that pushing treatment to toxicity undoubtedly produces may be alleviated by improved supportive treatment, and may be a price worth paying anyway in terms of overall long survival. Frequent neutropenia may paradoxically have the opposite effect if it leads to prolonged interruption of treatment, but this is a data derived hypothesis that needs confirmation from other studies.

Ideally, the suggestion that therapeutic myelosuppression can reduce the relapse rate in lymphoblastic leukaemia should be subjected to further clinical trial, but such a trial would be extremely difficult to structure, would require a degree of physician compliance unlikely to be achieved, and would be ethically questionable as it would be based on demonstrating an inferior result for half of the entrants. In the face of evidence already available it would seem reasonable to adopt the practice at this stage in all future regimens.

References

- ¹ Preliminary Report to the Medical Research Council by the

Leukaemia Committee and the Working Party on Leukaemia in Childhood. Treatment of acute lymphoblastic leukaemia. Comparison of immunotherapy (BCG), intermittent methotrexate and no therapy after a five-month intensive cytotoxic regimen (Concord trial). *Br Med J* 1971;iv:189-94.

- ² Report to the Council by the Working Party on Leukaemia in Childhood. Medical Research Council Leukaemia Trial—UKALL V: an attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia. *J Clin Oncol* 1986;4:1758-64.

- ³ Report to the Council by the Working Party on Leukaemia in Childhood. Improvement in treatment for children with acute lymphoblastic leukaemia. The Medical Research Council UKALL Trials, 1972-84. *Lancet* 1986;i:408-10.

- ⁴ Pinkel D, Hernandez K, Borella L, *et al*. Drug dosage and remission duration in childhood lymphocytic leukemia. *Cancer* 1971;27:247-56.

- ⁵ Van Eys J, Chen TT, Berry D, *et al*. The effect of drug dosage on outcome and infectious complications in the treatment of childhood lymphocytic leukemia. *Proceedings of the American Society for Clinical Oncology* 1981;22:478.

- ⁶ Schmiegelow K, Pulczynska MK, Siep M. White cell count during maintenance chemotherapy for standard-risk childhood acute lymphoblastic leukemia: relation to relapse rate. *Pediatric Hematology and Oncology* 1988;5:259-67.

- ⁷ Pinkel D. 6-Mercaptopurine dosage. *Lancet* 1987;ii:1267.

Correspondence to Dr JS Lilleyman, The Children's Hospital, Western Bank, Sheffield S10 2TH.

Accepted 10 March 1989