Short reports

A reappraisal of routine marrow examination therapy of acute lymphoblastic leukaemia

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SUMMARY Out of 557 routine marrow examinations performed in children receiving maintenance therapy, or having completed therapy, for acute lymphoblastic leukaemia or non-Hodgkin's lymphoma, only 9 marrow relapses were found. Out of 14 marrow examinations performed because of haematological or clinical indications of possible relapse, only 3 failed to confirm relapse. It is suggested that routine marrow examination to detect relapse is not worthwhile and should be stopped.

Modern treatment of acute lymphoblastic leukaemia (ALL) in childhood results in successful clinical and haematological remission in most children. If this is followed by central nervous system prophylaxis and combination maintenance chemotherapy, a disease-free survival rate of up to 50% at 5 years can be expected.¹ Although the optimum length of maintenance chemotherapy is not certain,² it is probably between 2 and 3 years.

Most protocols, including those of the UK ALL trials of the Medical Research Council, include routine bone marrow examination during maintenance therapy. In the UK ALL trials, bone marrow examinations are performed at 3-monthly intervals, timed to coincide with the start of each 12-week module in the maintenance schedules.

We realised that most marrow examinations carried out during maintenance therapy showed no evidence of leukaemia, and decided to find out how many marrow relapses were detected by routine marrow examinations.

Patients and methods

In the period January 1978 to December 1979, all routine marrow examinations carried out on children with ALL or non-Hodgkin's lymphoma (NHL), whether or not marrow was involved, were compared with peripheral blood counts taken simultaneously.

Most children were treated with standard UK ALL regimens, but a few of them were on the protocols devised by the United Kingdom Childhood Cancer Study Group for NHL.

For the purpose of this study, a routine marrow examination was defined as one performed in a patient on maintenance therapy, or in a patient who had completed maintenance therapy, and in whom there was no clinical evidence of disease. Children were included whether in first or subsequent remissions. Such examinations were performed every 12 weeks during chemotherapy. To avoid any distortion by including marrow examinations on children undergoing reinduction therapy after marrow relapse, only those patients whose last marrow examination had shown no evidence of leukaemia were included.

Dissemination to the marrow is not rare in children with NHL even though the marrow might seem normal at presentation.³ Such children had also been subjected to routine marrow examination during maintenance therapy in most protocols. It was therefore considered important to include such patients in this study, although by doing so only about 30 marrow examinations were contributed.

For the purpose of this study, a marrow examination was considered 'normal' if a differential count on a marrow smear showed <10% blast cells. While realising that the 5% level is the one currently used by most haematologists, it is our practice to view any blast cell count of between 5 and 10% as borderline and not as a frank relapse. A careful watch was generally kept in such cases and maintenance therapy continued. No estimates of marrow cellularity were considered in this study in the definition of normal. A marrow showing >10% blast cells was regarded as evidence of relapse, although in fact in most relapses marrows showed >30% blast cells.

A 'normal' peripheral blood count was defined in this study as one in which all values were equal to, or

greater than, the following: haemoglobin 10.5 g/dl , white cell count $2.5 \times 10^9/\text{l}$, platelet count $120 \times 10^9/\text{l}$. These values were chosen to take account of the cytopenia induced by maintenance therapy.

In this unit, the blood count is performed on a capillary sample and the result, including a differential white cell count, is obtained before the child is seen by the clinician. It was therefore possible to detect any child who had developed any haematological change, including circulating blast cells, since his last attendance.

A non-routine marrow examination was defined as one performed for any of the following reasons: circulating blast cells, bone pain, uncertain morphology, or an abnormal count without blast cells if relapse was suspected.

Most of the routine marrow examinations were carried out under a short halothane/oxygen/nitrous oxide anaesthetic, although many of the non-routine marrow examinations were performed under local anaesthesia.

Results

Five hundred and fifty-seven routine marrow examinations were performed (Table 1), only 9 (1.6%) showed relapse. These may be considered as unexpected relapses and it is significant that only 2 of these children had normal blood counts at the time of their marrow examination. The other 7 relapses showed varying degrees of cytopenia, but no circulating blast cells.

Forty-five (8%) of the routine marrow examinations were performed on children with peripheral blood counts at the time of marrow examination showing one, or more, haemoglobin value, white count, or platelet count below the 'normal' values used in this study. This cytopenia was considered to be a result of marrow depression by chemotherapy and none of these marrow examinations showed evidence of leukaemia.

Fourteen non-routine marrow examinations were performed (Table 2), only 3 failed to confirm marrow relapse. Two were performed because of pronounced peripheral blood cytopenia which was shown to be the result of drug-induced marrow depression. The third examination was performed because, although

Table 2 14 non-routine marrow examinations

Blood	Normal	Abnormal (with blasts)	Abnormal (no blasts)
Marrow	Relapse	Relapse	Normal
Number of marrow examinations	1	10	3

the peripheral counts were satisfactory, blast cells had been incorrectly reported in the blood film. The one marrow examination carried out in a child with normal counts was performed because of generalised bone pain and confirmed relapse.

All children with blast cells in the blood were shown on marrow examination to have indeed relapsed.

The analysis showed that 20 (3.5%) marrow relapses were detected out of 571 marrow examinations and 11 were found by non-routine marrow examination, generally as a result of finding circulating blast cells. The remaining 9 relapses were found on routine examinations. Six of these had abnormal counts with no blast cells, but a comparison of the actual values with those of the 45 (8%) marrow examinations who, by chance, had abnormal counts at the time of the routine marrow examination, unfortunately showed that the children in relapse could not be distinguished with certainty from those whose marrows did not show leukaemic infiltration. It was however, noted that platelet counts $<100 \times 10^9/\text{l}$ were more common, 50% (3 of 6) in those children who had indeed relapsed compared with 24% (11 of 45) in those with abnormal counts, but no evidence of relapse in the marrow. Only 2 children with 'normal' counts were shown on marrow examination to have relapsed, whereas 503 marrow examinations in children with 'normal' blood counts were performed to confirm the absence of relapse.

Discussion

The incidence of unexpected relapse on routine biopsy in children with 'normal' counts was 0.4%. If only children with abnormal counts, without circulating blasts, were to have routine marrow examinations performed the incidence of relapse would be 12% (6 in 52) which represents a 30-fold increase. However, this still means that about 9 out of every 10 such marrow examinations would not show relapse. If it could be shown that detection of marrow relapse before circulating blast cells are seen would result in a better reinduction rate or longer second remission, one could perhaps argue more strongly that routine marrow examination was valuable.

Table 1 557 routine marrow examinations

Blood	Normal	Normal	Abnormal (no blasts)
Marrow	Normal	Relapse	Normal Relapse
Number of marrow examinations	503	2	45 7

In this small series of 20 relapses (11 detected by non-routine marrow examination, 9 by routine examination), 8 children in the first group and 6 in the second group achieved a second remission.

Because of the small number of patients no useful comment can be made about the duration of the second remission. However, in view of the overall poor prognosis of children with ALL who have bone marrow relapses during treatment,⁴ or after treatment has stopped,⁵ it seems improbable that overall survival after relapse would be much, if at all, reduced by the abolition of routine marrow examinations. It should be stressed that each child in this study, by the design of the study, had had a normal marrow examination at least 12 weeks before.

The figures presented in this study show that routine marrow examination every 3 months in children with ALL or NHL has a low (0.4%) relapse yield if the peripheral count is normal; even if the count is abnormal, without circulating blast cells, the yield only increases to a modest 12%.

It is therefore suggested that routine marrow examination during maintenance therapy is not worth while and should not be included in the protocols of future studies. The clinician must obviously establish remission in a new case after induction therapy and should not hesitate to proceed to marrow examination in a child in remission whose peripheral counts indicate cause for concern.

It is hoped that the well-known trauma to child,

parents, and doctor of performing a marrow examination in a conscious or poorly-sedated child will be lessened by the abolition of routine marrow examination. In addition the small, but ever present, risk of a general anaesthetic in those units fortunate enough to have such a service, will be lessened even further by the administration of fewer anaesthetics.

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References

- 1 Hardisty R M, Chessells J M. Acute leukaemia in childhood. Management and prognosis. In: Hoffbrand A V, Brain M C, Hirsh J, eds. *Recent advances in haematology*. Vol. 2. Edinburgh: Churchill Livingstone, 1977: 159-73.
- 2 Medical Research Council Working Party on Leukaemia in Childhood. Effects of varying radiation schedule, cyclophosphamide treatment, and duration of treatment in acute lymphoblastic leukaemia. *Br Med J* 1978; ii: 787-91.
- 3 Jones B, Klingberg W G. Lymphosarcoma in children. *J Pediatr* 1963; 63: 11-20.
- 4 Cornbleet M A, Chessells J M. Bone marrow relapse in acute lymphoblastic leukaemia in childhood. *Br Med J* 1978; ii: 104-6.
- 5 Rivera G, Pratt C B, Aur J A R, Verzosa M, Hustu H O. Recurrent childhood lymphocytic leukaemia following cessation of therapy. *Cancer* 1976; 37: 1679-86.

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Congenital villous atrophy associated with stagnant loop syndrome

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SUMMARY A child who presented at age 9 months with steatorrhoea and malnutrition is described. After an initial period of intravenous feeding it was found that oral gentamicin led to a reduction of clinical steatorrhoea and an increase in weight, and so gentamicin was continued for 18 months. Investigation showed severe villous atrophy without pronounced inflammatory cell infiltrate and with no increase in intraepithelial lymphocytes. The villous atrophy was not present in the duodenum but started in the jejunum. The small-intestine was radiologically dilated throughout its length. It is suggested that this structurally-abnormal gut acted as a stagnant loop and exacerbated the steatorrhoea.

Intractable diarrhoea of infancy has many causes¹ and a high mortality. The child described in this report had intractable diarrhoea and presented with malnutrition at age 9 months. Her life was saved by a period of intravenous feeding. Subsequent investigation showed an unusual enteropathy.

Case report

This baby girl was born at 32 weeks' gestational age (birthweight 1.56 kg) by spontaneous vertex delivery and there were no neonatal problems. At age 2 months, she was discharged home with a weight of 2.41 kg. There had been no diarrhoea and she was fed on Cow and Gate Baby Milk Plus.