Prognostic significance of radiological bone involvement in childhood acute lymphoblastic leukaemia

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SUMMARY In 98 children with acute lymphoblastic leukaemia, aged 1 to 12 years, the prognostic significance of radiological bone involvement was studied. The mean duration of remission and of survival was much shorter in cases with multiple bone involvement (3 or more bones) than in those where bone involvement was absent. In those cases presenting with 1 or 2 bone lesions no statement of prognostic significance can be made at this stage. A radiological skeletal survey should be made in all children presenting with leukaemia to identify those (about 15%) having multiple bone lesions and therefore a poor prognosis, in order that they can be given more intensive therapy.

The outlook for leukaemic patients where there is early bone involvement has been reported to be unfavourable in some series but not in others (Kundel et al., 1964; Nies et al., 1965; Aur et al., 1972). We have analysed a series of 98 children with acute lymphoblastic leukaemia (ALL), with a view to answering two questions. (1) Does leukaemic bone involvement correlate with the course of ALL? (2) Is there a syndrome in which diffuse skeletal lesions combined with characteristic haematological and clinical findings imply a poor prognosis?

Materials and methods

Ninety-eight children with ALL, between the ages of 1 and 12 years were followed between 1963 and 1975. Any one of the following radiological changes in bones were considered as leukaemic. (1) Meta-

We also considered the following factors: age, sex, number of skeletal lesions, bone pain, WBC count, the interval between the first onset of symptoms and haematological diagnosis, response to therapy, median duration of complete remission, and median survival. Each factor was analysed statistically, using parametric (Linton and Gallo, 1975) and nonparametric (Ryan, 1959; Linton and Gallo, 1975) tests. The usual methodology for determining curves and standard errors (SE) of the median period of remission and survival times was used. All patients were treated similarly, regardless of the presence or absence of bone lesions. The treatment regimens used over this 12-year period may be summarized as follows.

1963–1965 prednisone, 6-mercaptopurine, and methotrexate (6MP-MTX); no prophylactic treat-

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Table  Summary of data in 98 cases of ALL

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Comparisons</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 48</td>
<td>n = 34</td>
<td>n = 16</td>
<td></td>
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<tr>
<td>Median duration of complete remission (m)</td>
<td>25-3</td>
<td>17-4</td>
<td>7-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>NS</td>
<td>I vs 0</td>
<td>NS</td>
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<tr>
<td></td>
<td>0 vs II</td>
<td>&lt;0.05</td>
<td>I vs II</td>
<td>NS</td>
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<tr>
<td></td>
<td>I vs 0</td>
<td>NS</td>
<td>0 vs II</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median survival (m)</td>
<td>42</td>
<td>31-4</td>
<td>18-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>NS</td>
<td>I vs 0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0 vs II</td>
<td>&lt;0.05</td>
<td>I vs II</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>I vs 0</td>
<td>NS</td>
<td>0 vs II</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Complete remission (%)</td>
<td>90</td>
<td>94</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>NS</td>
<td>I vs 0</td>
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<td></td>
<td>0 vs II</td>
<td>NS</td>
<td>I vs II</td>
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<tr>
<td></td>
<td>I vs 0</td>
<td>NS</td>
<td>0 vs II</td>
<td>NS</td>
</tr>
<tr>
<td>Interval between the first symptoms and diagnosis (days) (mean ± SE)</td>
<td>43.12 ± 6.84</td>
<td>36.39 ± 8.39</td>
<td>166.07 ± 38.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>&lt;0.01</td>
<td>I vs 0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>0 vs II</td>
<td>&lt;0.01</td>
<td>0 vs II</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>I vs 0</td>
<td>NS</td>
<td>0 vs II</td>
<td>NS</td>
</tr>
<tr>
<td>Bone pain (%)</td>
<td>12</td>
<td>38</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>NS</td>
<td>I vs 0</td>
<td>NS</td>
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<td></td>
<td>0 vs II</td>
<td>NS</td>
<td>I vs 0</td>
<td>NS</td>
</tr>
<tr>
<td>WBC count (× 10⁹/l) (mean ± SE)</td>
<td>61.54 ± 18.09</td>
<td>31.16 ± 8.84</td>
<td>14.15 ± 5.01</td>
<td></td>
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<tr>
<td></td>
<td>I vs II</td>
<td>&lt;0.01</td>
<td>I vs 0</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>0 vs II</td>
<td>&lt;0.01</td>
<td>0 vs II</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% of cases in different groups</td>
<td>49</td>
<td>35</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age (years) (mean ± SE)</td>
<td>5.5 ± 0.44</td>
<td>3.94 ± 0.36</td>
<td>6.56 ± 0.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I vs II</td>
<td>&lt;0.01</td>
<td>I vs 0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>0 vs II</td>
<td>NS</td>
<td>0 vs II</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>30/18</td>
<td>22/12</td>
<td>8/8</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1  Median duration of complete remission.

Fig. 2  Median survival.

pared with group 0 (25.3 months). No significant difference was found between groups 0 and I (17.4 months) or between groups I and II. Median survival time (Fig. 2) also showed a significant difference when group II (18.4 months) was compared with group 0 (42 months). Remission induction rate: the percentage of patients who attained complete remission did not differ between the three groups. Interval between onset of symptoms (bone pain, fever, anaemia, haemorrhagic manifestations) and haematological diagnosis of ALL: for group II (166 days) this was longer (P < 0.01) than in groups 0 (43 days) or I (37 days) (Kruskal-Wallis statistical test and Ryan's procedure in combination). Incidence of bone pain: this was highest in group II, lowest in group 0, and intermediate in group I (Fisher's exact test). WBC count: though the median value was 61.540/mm³ (61.54 × 10⁹/l) in group 0, 31.160/mm³ (31.16 × 10⁹/l) in group I, and 14.150/mm³ (14.15 × 10⁹/l) in group II, there were no significant differences between the three groups. This was perhaps due to the use of a nonparametric test (Kruskal-Wallis test) which was necessary because of the variability of the data.

Frequency and type of skeletal lesions: in 50 of the patients the x-ray findings were characteristic of leukaemia. 34 of the 50 had lesions limited to 1 or 2 skeletal segments (group I), but the other 16 had involvement of more than 2 segments. The fre-
quency with which various bones were involved is 
shown in Fig. 3. Age: there was no significant 
difference (Duncan's new multiple range test), 
between groups 0 (5·5 years) and II (6·6 years), 
but the differences between groups I (3·9 years) and 
II and between groups I and 0 were significant. 
Sex: there was no significant difference between 
the three groups (group 0, 63% males, group I, 65% and 
group II, 50%).

Fig. 3 Sites and types of bone lesions found in 98 
children presenting with acute lymphocytic leukaemia.

Discussion

Selection of those ALL cases with an unfavourable 
prognosis, with a view to giving them intensive 
therapy without exposing the other patients to the 
risk of such treatment, is an aim which is generally 
recognized (Miller, 1975), but the possible prognostic 
significance of skeletal lesions has not been much 
studied. Kundel et al. (1964) drew attention to the 
fact that certain cases of leukaemia characterized by 
bone pain, bone necrosis, and leucopenia responded 
poorly to therapy. Nies et al. (1965) confirmed this 
in a large retrospective study of 316 patients 
examined post mortem, and they suggested that such 
cases might represent a particular clinicopathological

complex. Aur et al. (1972), however, in a study of 221 
children with ALL found no correlation between 
initial radiological bone involvement and prognosis, 
while Khanna et al. (1975), on the basis of 5 cases of 
ALL with diffuse skeletal lesions suggested that the 
presence of such lesions was associated with a short 
survival time. We have reconsidered the problem, 
comparing cases with multiple skeletal involvement 
(group II) with those having either no bone lesions 
(group 0) or lesions in only 1 or 2 skeletal segments 
(group I). One firm conclusion emerged, group II 
were found to have significantly shorter durations of 
both complete remission and survival when 
compared with group 0.

Despite the marked differences between groups I 
and II in the duration of complete remission (group 
II, 7·4 months; group I, 17·4 months) and in median 
survival time (group II, 18·4 months; group I, 31·4 months), these differences failed to attain 
statistical significance, possibly due to the small 
number of cases. Again, when comparing group 0 
with group I no statistically significant differences 
were shown. The prognostic significance of the 
presence of 1 or 2 bone lesions remains therefore 
undecided.

The possible association of other haematological 
and clinical findings with skeletal lesions, as 
suggested by Nies et al. (1965), was also studied. We 
confirmed that the form of childhood ALL which 
prevents with extensive skeletal lesions with severe 
and constant pain, a long interval between the onset 
of first symptoms and haematological diagnosis, and 
leucopenia, carries an unfavourable outlook. 16% 
of our cases fell into this pattern, in agreement with 
the figure of 15% given by Kundel et al. (1964) and 
Nies et al. (1965). Thus about 15% of cases of 
childhood ALL will present with this recognizable 
clinico-haematological pattern carrying a predictably 
poor prognosis. It therefore seems important to 
make a complete radiological skeletal survey in 
every case of ALL in order to identify this group of 
cases which will merit more intensive therapy.

References

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