Cyclic chemotherapy in acute lymphoblastic leukaemia of childhood

5-year survivals

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Vowels, M. R., and Willoughby, M. L. N. (1973). Archives of Disease in Childhood, 48, 436. Cyclic chemotherapy in acute lymphoblastic leukaemia: 5-year survivals. Of 31 children with acute lymphoblastic leukaemia treated with a cyclical scheme of chemotherapy, 19% survived for over 5 years, 16% remained in continuing haematological remission for 5 years, and 13% remained leukaemia free for 5 years. These findings are relevant to potential cure, unlike the median remission duration, which is a measure of palliation.

A relation between the percentage of PAS-positive blast cells at diagnosis and duration of control of the disease still pertains for the long-term results in this series of patients.

Between 1964 and 1967, 31 children with acute lymphoblastic leukaemia (ALL) were treated according to the drug schedule shown in Fig. 1A. 6-Mercaptopurine, methotrexate, and cyclophosphamide were given in cyclical rotation at conventional doses for maintenance of remission. The median length of first remission was 13 months (Willoughby and Laurie, 1968). Whereas the median length of first remission is a valid measurement of palliative therapy, it is the percentage surviving and in remission at 5 years or more that is relevant to cure.

It is now possible to see the long-term results of this therapy, since the last patient was placed upon the schedule over 5 years ago. These results are of interest (1) because they show a marked increase in 5-year survival over that of the preceding chemotherapeutic era, and (2) because they provide a yardstick against which recent and future more complex schedules can be compared in terms of 5-year results.

Clinical materials and methods

These were as described earlier (Willoughby and Laurie, 1968). The drug therapy was as shown in Fig. 1A, except that this was modified in two ways after mid-1967. (a) Twice-weekly oral high-dose methotrexate was substituted in place of daily low-dose methotrexate; (b) 6-monthly vincristine plus prednisolone 'pseudoreinduction' courses were superimposed upon the cyclic schedule. These changes are shown in Fig. 1B. A marrow examination was performed on the first day of each pseudoreinduction course. Assessment of PAS-positivity of the blast cells in the marrow at diagnosis was performed as described by Laurie (1968).

Results

All 31 patients with ALL who were placed on this schedule achieved complete remission and there were, therefore, no exclusions on grounds of early death or failure to attain remission. Fig. 2 shows the curves of complete remission duration and of total survival. Complete remission was terminated by either haematological or meningeal relapse and, in 2 patients, by death from infection while in remission. Median duration of complete remission is 13 months, and of survival 20 months, neither having changed since the original report. The long-term results now available show that 6 patients (19·5%) survived for 5 years or more. 5 of these (16%) remained in continuing haematological remission, while the sixth survived 5 years in spite of repeated relapses, the first of which occurred at 42 months from diagnosis. Of the 5 who were still in haematological remission at 5 years, 1 had a meningeal relapse at 42 months and a subsequent haematological relapse at 66 months. Thus,
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A

6-MP ——— MTX ——— CYCLO
2.5mg/kg per day 0.125mg/kg per day 3.5mg/kg per day

10wk ——— 6wk ——— 6wk

5 month cycle

B

6-MP ——— MTX ——— CYCLO
70mg/m² per day 20mg/m² 75mg/m² per day
twice-weekly

10wk ——— 6wk ——— 6wk

5 month cycle

Vincristine
1.5mg/m² I.V. weekly x 2 +

Prednisolone
60mg/day for 2 weeks, then tailed off

Superimposed at 5½ to 6-monthly intervals

Fig. 1.—Maintenance cyclic chemotherapy schedules. A, As used from 1964 to mid-1967. B, As used since mid-1967 with superimposed ‘pseudoreinduction’ courses at approximately 6-monthly intervals. This chemotherapy followed initial remission induction with prednisolone ± 6-MP ± vincristine. 6-MP, 6-mercaptopurine; MTX, methotrexate; Cyclo, cyclophosphamide.

4 patients (13%) remained leukaemia free for 5 years or more. Of these, 1 died after 63 months of continuing remission from overwhelming chickenpox while taking methotrexate, and 3 still remain leukaemia free at 68, 92, and 104 months. Chemotherapy is currently being stopped when 96 months have been reached.

A second patient died from infection (probable encephalitis) while still in his first remission at 27 months. This has resulted in an incidence in this series of mortality from infection of 6.4% among patients in complete remission and on maintenance therapy.

Table I shows the haematological status in the 31 patients at diagnosis, comparing those who survived longer than the median with those who survived for a shorter period. A high blast cell count and low platelet count in the peripheral blood were found in those with a shorter survival. Table I also shows that a higher proportion of the leukaemic blast cells in the marrow at diagnosis were PAS-positive in those surviving longer. Fig. 3 shows that none of the patients with less than 35% PAS-positive blast cells survived beyond the median, whereas 11 out of 16 with over 35% PAS-positive blast cells survived beyond the median ($\chi^2=9.4$, $P < 0.01$).

Discussion

Of the haematological parameters found at diagnosis (Table I), the high white and blast cell counts and lower platelet count in patients destined to have remission shorter than the median have already been shown by others (Acute Leukemia
Group B, 1963; Zuelzer, 1964). In reviewing the long-term results in this series of patients it was also of interest to see if the relation between percentage PAS-positive blast cells at diagnosis and the duration of subsequent survival as originally described by Laurie (1968) still pertained. As seen in Table I and Fig. 3, this correlation does still exist. A similar relation has also been found by the Medical Research Council (unpublished data, 1969) among children with ALL on maintenance therapy with conventional doses of mercaptopurine and methotrexate. This was not found, however, by Bennett and Henderson (1969) in patients receiving high-dose combination chemotherapy (POMP). It is possible that certain innate characteristics of the leukaemia cell line are altered by intensive chemotherapy, but not by the milder therapy used in the present series and the early MRC trials.

From a study of 127 long-term survivors, Burchenal (1968) estimated that the 5-year survival rate in childhood acute leukaemia lay between 0·1 and 1·0% for those diagnosed between approximately 1951 and 1963. Till and Hardisty (1972), from a similar study in the U.K., suggested that the 4-year survival rate was approximately 1·5% for those diagnosed during the period 1953–67, but that the rate appeared to have doubled over the last 5 years of this period. By contrast, there have been a number of reports, largely from American groups and summarized by Pinkel (1971), where multiple antileukaemic drugs have been used in remission, either cyclically or in combination, and where higher rates of 5-year survival and 5-year remission have been obtained (Table II). The best 5-year results are those of Pinkel (1971) with 17% in complete remission and 19% surviving, while a 5-year survival rate of approximately 16%, has been reported from Acute Leukemia Group B (Holland, 1971). The results obtained with the cyclical therapy schedule shown in Fig. 1A and B are closely comparable with the more recent American series, and very different from those of the previous chemotherapeutic era either in the U.K. (Till and Hardisty, 1972) or elsewhere (Burchenal, 1968). In its simplest form the superior long-term results and possible cure are perhaps due to the use of multiple antileukaemic drugs during the period of continuing remission. Appreciation of the likelihood that 1 in 5 patients will survive 5 years and that 1 in 6 may be cured should encourage maximum

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**TABLE I**

*Haematological data at diagnosis*

<table>
<thead>
<tr>
<th>Survival</th>
<th>Peripheral blood</th>
<th>Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC/mm³ (log mean ± SD)</td>
<td>Blasts/mm³ (log mean ± SD)</td>
</tr>
<tr>
<td>&lt; 20 mth</td>
<td>28,400 ± 25,500</td>
<td>11,800 ± 10,300</td>
</tr>
<tr>
<td>15 patients</td>
<td>&gt; 20 mth</td>
<td>5,200 ± 3,500</td>
</tr>
</tbody>
</table>

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**Fig. 3.—Relation between percentage of PAS-positive marrow blast cells at diagnosis and subsequent survival.** The number of patients with above or below 35% PAS-positive cells have been classified in a '2 × 2 table' according to whether they survived longer or shorter than the median duration.
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TABLE II
5-year complete remission and survival rates for childhood acute lymphoblastic leukaemia*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Remission induction</th>
<th>Remission maintenance</th>
<th>Years of patient intake</th>
<th>Initial no. of patients</th>
<th>5-year complete remission total (%)</th>
<th>5-year survival total (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred, 6-MP</td>
<td>Cyclic</td>
<td>6-MP, MTX, Pred</td>
<td>55-64</td>
<td>175</td>
<td>6 (3.4)</td>
<td>7 (4.0)</td>
<td>Zuelzer, 1964</td>
</tr>
<tr>
<td>Pred, 6-MP</td>
<td>Sequential</td>
<td>6-MP, MTX, Cyclo, VCR</td>
<td>59-65</td>
<td>71</td>
<td>-</td>
<td>4 (5.6)</td>
<td>Saunders, Kauder, and Mauer (1967)</td>
</tr>
<tr>
<td>Pred, MTX or 6-MP</td>
<td>Cyclic or sequential</td>
<td>MTX, VCR, Pred, Cyclo, 6-MP</td>
<td>63-69</td>
<td>229</td>
<td>12 (5.2)</td>
<td>-</td>
<td>Krivit, Gilchrist, and Beatty (1970)</td>
</tr>
<tr>
<td>Pred, VCR, 6-MP, MTX</td>
<td>Monthly</td>
<td>POMP</td>
<td>64-67</td>
<td>35</td>
<td>2 (5.7)</td>
<td>2 (5.7)</td>
<td>Henderson and Samaha (1969)</td>
</tr>
<tr>
<td>Pred ± 6-MP ± VCR</td>
<td>Combination</td>
<td>MTX, Cyclo, VCR, CNS radiation 500-1200r</td>
<td>62-65</td>
<td>41</td>
<td>7 (17.0)</td>
<td>8 (19.0)</td>
<td>Pinkel (1971) (total therapy) 1-III</td>
</tr>
</tbody>
</table>

*Data partly derived from Pinkel (1971). Pred, prednisolone or prednisone; VCR, vincristine; 6-MP, 6-mercaptopurine; MTX, methotrexate; Cyclo, cyclophosphamide; POMP, 5-day high-dose courses of prednisone x 5, 6-MP x 5, MTX x 5, VCR x 1.

Fig. 4.—Complete remission duration curves for various published chemotherapy schedules giving long-term results in childhood acute lymphoblastic leukaemia. Numerical fractions indicate the number of patients still in remission at cut off and the number of patients entering the schedule.

Data for curves derived as follows. POMP, Henderson and Samaha (1969); Cyclic, present series; Pinkel III, George et al. (1968); Pinkel V, Aur et al. (1971) and Lancet (1972); ALGB 6801, Sinks (1972). *Best arm of 6801 protocol.
effort to achieve safe passage through the hazardous first weeks of remission induction therapy and to ensure that arrangements are made for optimum subsequent therapy. There was less force to this argument when fewer than 1% survived 5 years.

Two more recent American series, employing CNS prophylaxis and multiple-drug maintenance therapy, but for which 5-year results are not yet available, appear to be achieving even superior results which, by extrapolation, are likely to give 5-year remission rates in the region of 40% (Fig. 4).

REFERENCES


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