**Haematology and Blood Transfusion** Vol. 26
Modern Trends in Human Leukemia IV
Edited by Neth, Gallo, Graf, Mannweiler, Winkler


# Present Problems in Management of Childhood Lymphoblastic Leukaemia: Experience from the Hospital for Sick Children, London

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The majority of children with acute lymphoblastic leukaemia (ALL) at the Hospital for Sick Children, Great Ormond Street (GOS), are treated in collaborative protocols designed by the United Kingdom Medical Research Council Working Party on Childhood Leukaemia (UKALL trials). Data is presented from patients treated in these trials and in other protocols piloted at GOS for the Working Party.

In the late 1960s children with ALL were treated at GOS with a variety of sequential regimes or short intensive protocols such as the CONCORD (Medical Research Council 1971). Continuing chemotherapy (remission maintenance) with multiple agents as in UKALL I (Medical Research Council 1973) was introduced in 1970 and from 1972 onwards all patients received prophylaxis against development of leukaemic infiltration of the central nervous system (CNS) with cranial irradiation (2400 rads) and a course of intrathecal methotrexate injections and/or spinal irradiation. Long-term follow up of these patients has, as expected, confirmed that CNS prophylaxis increases the proportion of patients achieving long-term *disease-free* survival but has, as yet, failed to show any influence of

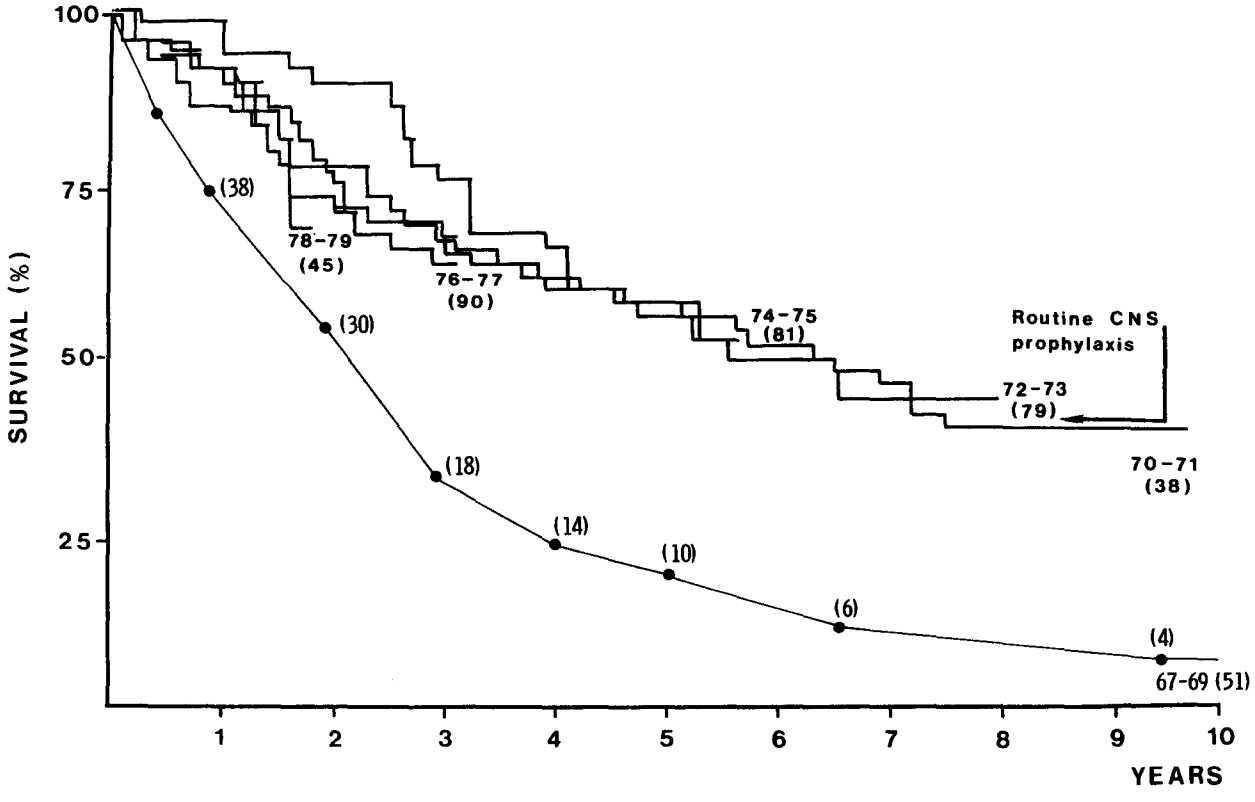


**Fig. 1.** Survival in all patients with ALL treated in consecutive periods at GOS. *Numbers in parentheses* refer to total numbers of patients in the period

CNS prophylaxis on overall survival or on duration of haematological remission (Figs. 1,2). The major problem in management, therefore, remains that of haematological relapse, although the proportion of deaths in remission also gives cause for continuing concern.

## A. Death in remission

Analysis of data from the first and second UKALL trials showed that death in remission was primarily seen in patients with "standard" prognostic features (aged less than 14 at diagnosis with a pre-treatment leucocyte count of less than $20 \times 10^9/1$) (Medical Research Council 1976). A survey of remission deaths in children at GOS between 1973 and 1977 (Table 1) who all received standard CNS prophylaxis with cranial irradiation and intrathecal methotrexate showed that the most common cause was measles pneumonia, usually occurring in children without overt clinical measles. Two of the four deaths from septicaemia occurred in young infants and one in a splenectomized child receiving prophylactic penicillin. The high incidence of measles pneumonia can be ascribed to the regrettably low uptake of measles vaccine in Britain.

**Table 1.** Causes of death in remission in 168 children with ALL

| Cause | No. patients |
|---|---|
| Measles | 6 |
| Septicaemia | 4 |
| Cytomegalovirus | 2 |
| Herpes simplex | 1 |
| Varicella-zoster | 1 |
| Total | 14 (8% of cases) |

Concern about these complications of treatment led us to explore the relative efficacy and immunosuppression of 6-mercaptopurine and methotrexate given in equivalent dose either continously or intermittently in a 5-day course every three weeks (Fig. 3). The continuous (C) and intermittent (I) arms of this protocol for "standard risk" patients were introduced at GOS in 1974 and the protocol was subsequently adopted as the UKALL V schedule, with introduction of an intermediate (G) schedule. The results of the immunological studies in the three groups of patients have recently been published (Rapson et al. 1980) and show that in patients receiving continuous chemotherapy the blood lymphocyte counts,

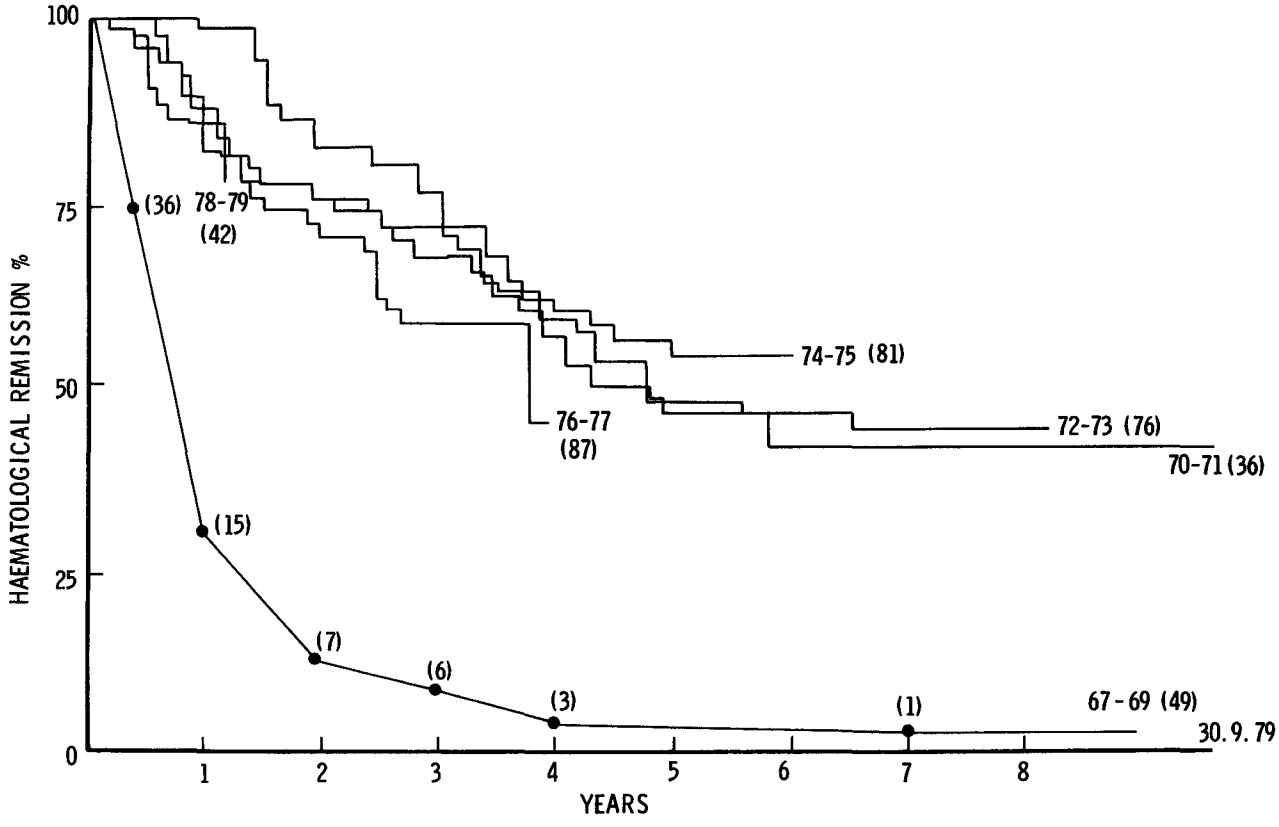


**Fig. 2.** Duration of first haematological remission in the same group of patients. The improvement between 1969 and 1970 is due to introduction of combination chemotherapy for remission maintenance

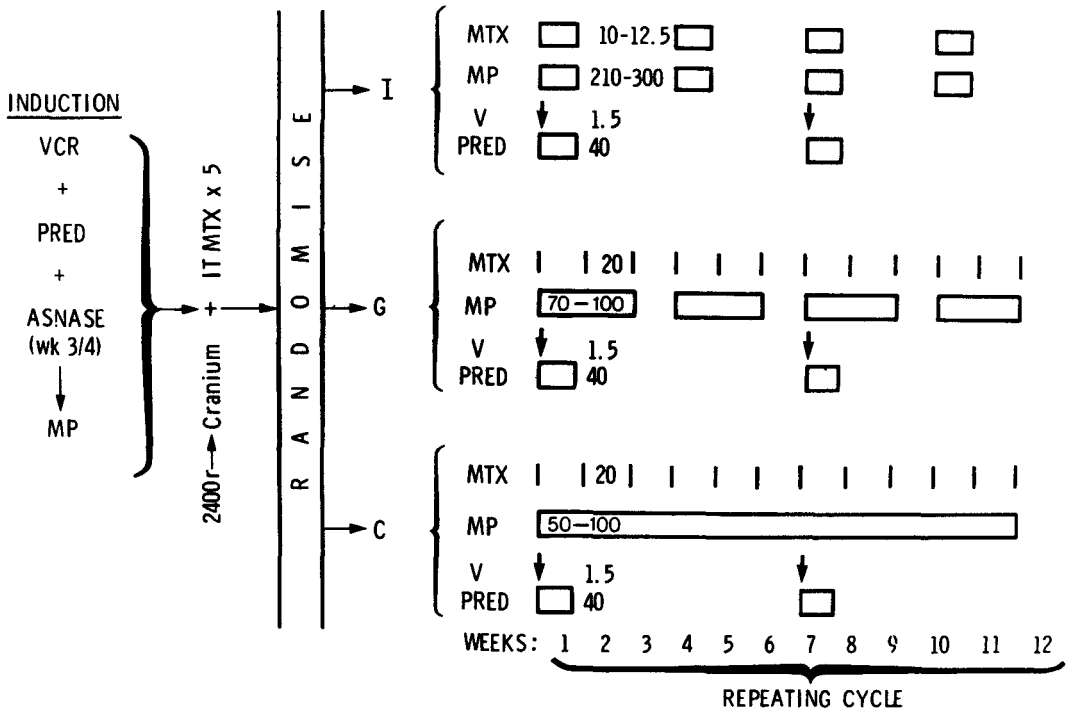


**Fig. 3.** Design of MRC UKALL V started at GOS in 1974. Doses of drugs are in mg/m$^2$ surface area. *Pred*, prednisolone; *V, VCR*, vincristine; *MTX*, methotrexate; and *MP*, 6-mercaptopurine

mitotic response to phytohaemagglutinin and plasma immunoglobulin levels were significantly lower than in patients receiving intermittent therapy. Results in the intermediate G group fell between the other two groups. We have subsequently reviewed the incidence of infection in 115 patients (Table 2) as of January 1980. Patients receiving continuous chemotherapy had a higher incidence of remission deaths, with measles again as the most common agent. The death from measles in the G group occurred in a patient in the first treatment cycle after radiotherapy. The two children in the study who survived measles were both receiving intermittent chemotherapy and in both the illness pursued a normal clinical course. Pneumocystis infection was confined to the C group but all cases responded to treatment with high dose co-trimoxazole.

Preliminary analysis of remission duration in the three groups of patients shows no significant differences between the three regimes, although schedule I appears marginally inferior (Fig. 4). However, schedule I has also been associated with nausea and mouth ulceration. Because of this, it has proved difficult to achieve the maximum drug dosage in all patients; the intermediate (G) schedule has been adopted for continuing chemotherapy in a subsequent protocol, and we are now starting a program of routine administration of immunoglobulin to all children at risk of measles.

**Table 2.** Infections in UKALL V pilot study

| Protocol | C | I | G | Total patients |
|---|---|---|---|---|
| No. patients | 55 | 37 | 23 | 115 |
| Admitted with infection | 29 | 1 | 9 | 39 |
| Pneumocystis | 7 | 0 | 0 | 7 |
| Deaths in remission (measles) | 6(4) | 0 | 2(1) | 8 |

## B. Prevention of Marrow Relapse

While these attempts to reduce remission deaths were in progress, the UKALL IV protocol for high risk patients compared the value of early intensive induction with cyclophosphamide, cytosine arabinoside, prednisolone and vincristine to a regime of prednisolone and vincristine (Fig. 5) and compared simple continuing chemotherapy as given in UKALL II (Medical Research Council 1976) with a rotating intermittent multiple drug schedule (Fig. 6). Preliminary analysis of the

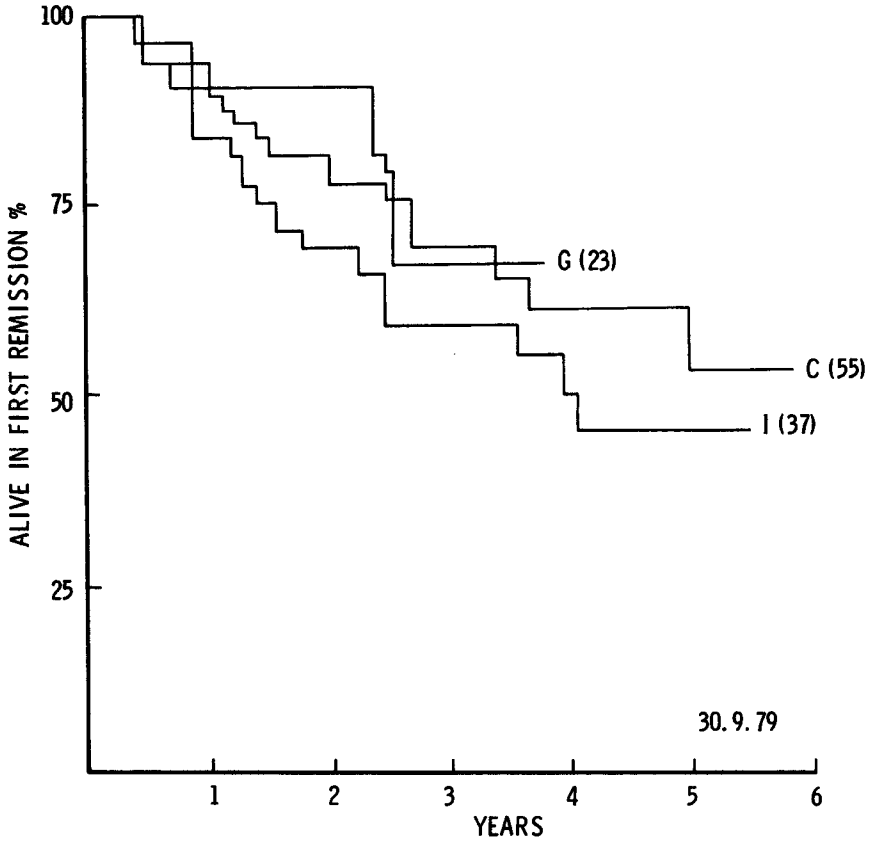


**Fig. 4.** Duration of first remission in patients on UKALL V schedule. *Numbers in parentheses* refer to total numbers of patients in each group

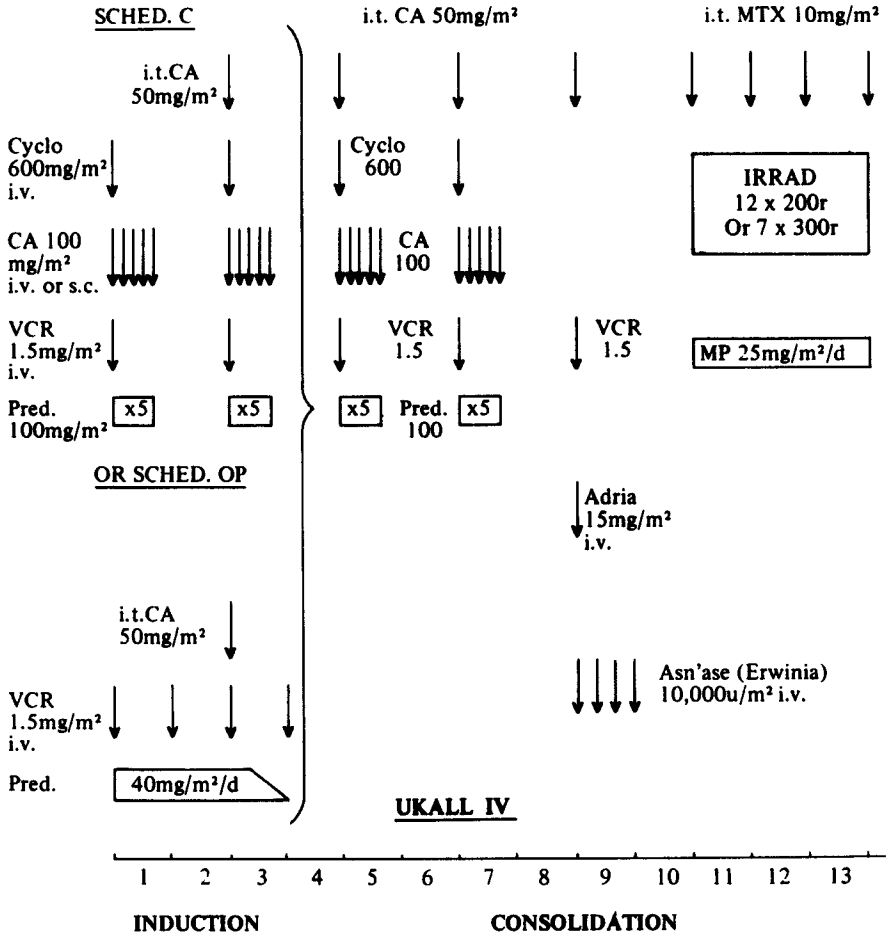


**Fig. 5.** MRC UKALL IV poor risk patients). Induction regimen with randomization to prednisolone and vincristine or COAP combination chemotherapy. *Cyclo*, cyclophosphamide; *CA*, cytosine arabinoside, *VCR*, vincristine; *Pred*, prednisolone; *Adria*, adriamycin; *MTX*, methotrexate; *MP*, 6-mercaptopurine

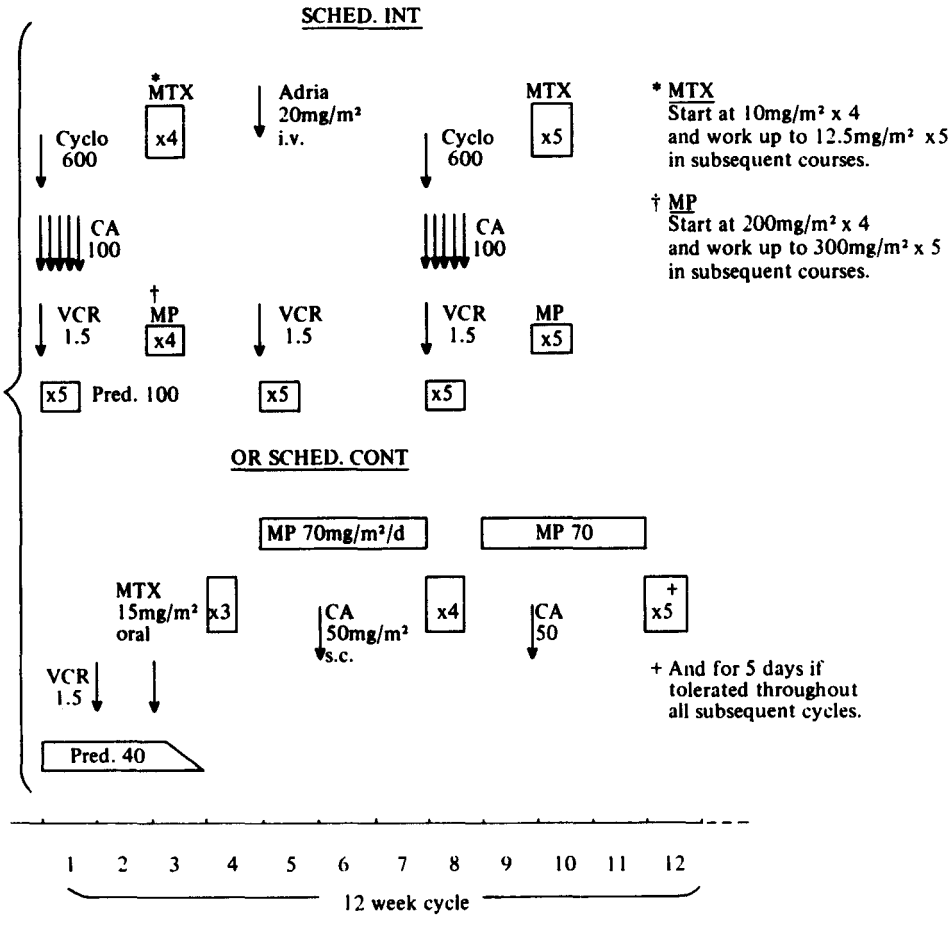


**Fig. 6.** UKALL IV continuing (maintenance) therapy. Abbreviations as in Figure 5

results is disappointing and shows no advantage for intensive induction or for multiple agent maintenance over the simpler schedules.

These drugs, of course, may not be the optimal ones to use in early induction. We have found that prolonged L-asparaginase in combination with daunorubicin, prednisolone and vincristine is extremely effective in relapsed and resistant ALL (Chessells and Cornbleet 1979) and are at present evaluating this combination of drugs in induction of first remission, with the aim of improving duration of subsequent haematological remission.

## C. Sex and Prognosis

Long-term follow up of the MRC UKALL II trial showed that boys fared significantly worse than girls and that this trend was not just due to testicular relapse (Medical Research Council 1978). Similar results have since been reported by others (George et al. 1979). This worse prognosis in boys has been consistently observed in our clinic population (Fig. 7) and is not confined to "poor risk" patients among whom there might be a predominance of T-cell ALL (Chessells 1979). The difference is accounted for partly but not entirely by testicular relapse; boys also have a higher incidence of marrow relapse after stopping treatment than girls (Fig. 8).

The influence of sex on prognosis, unlike that of leucocyte count or the immunological sub-type of the leukaemia (Chessells et al. 1977), becomes apparent well after the first year of treatment at about the time of stopping therapy.

We have two approaches to this problem at present. First, by early intensification of chemotherapy, as previously described, we are attempting to reduce the incidence of marrow relapse. Secondly, we are attempting to detect testicular disease early by routine bilateral wedge biopsy of the testicles in all boys at the time of stopping treatment. So far routine biopsy has been performed in 60 boys with no clinical sign of infiltration; infiltration was histologically detected in six (10%). Three of 54 boys with a negative biopsy have subse-

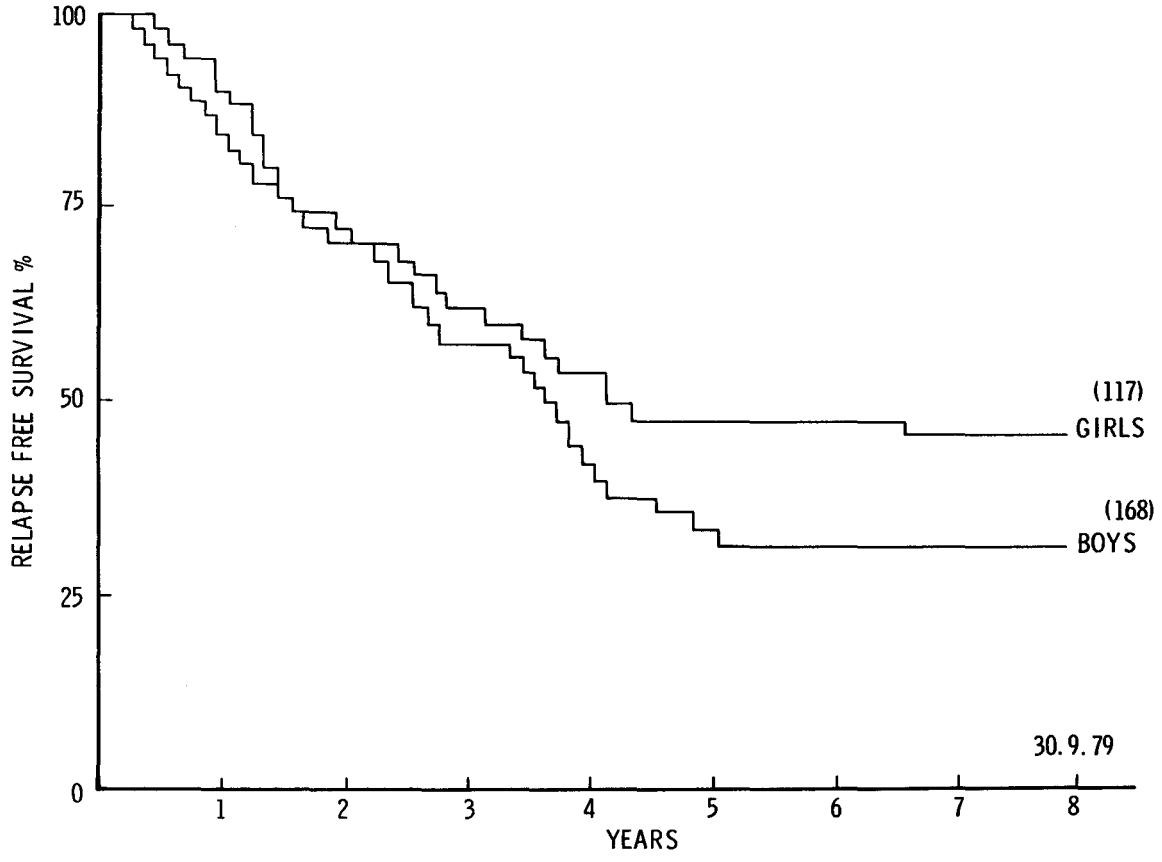


**Fig. 7.** Relapse-free survival compared in the sexes. GOS 1972–78. Note divergence at 3–5 years

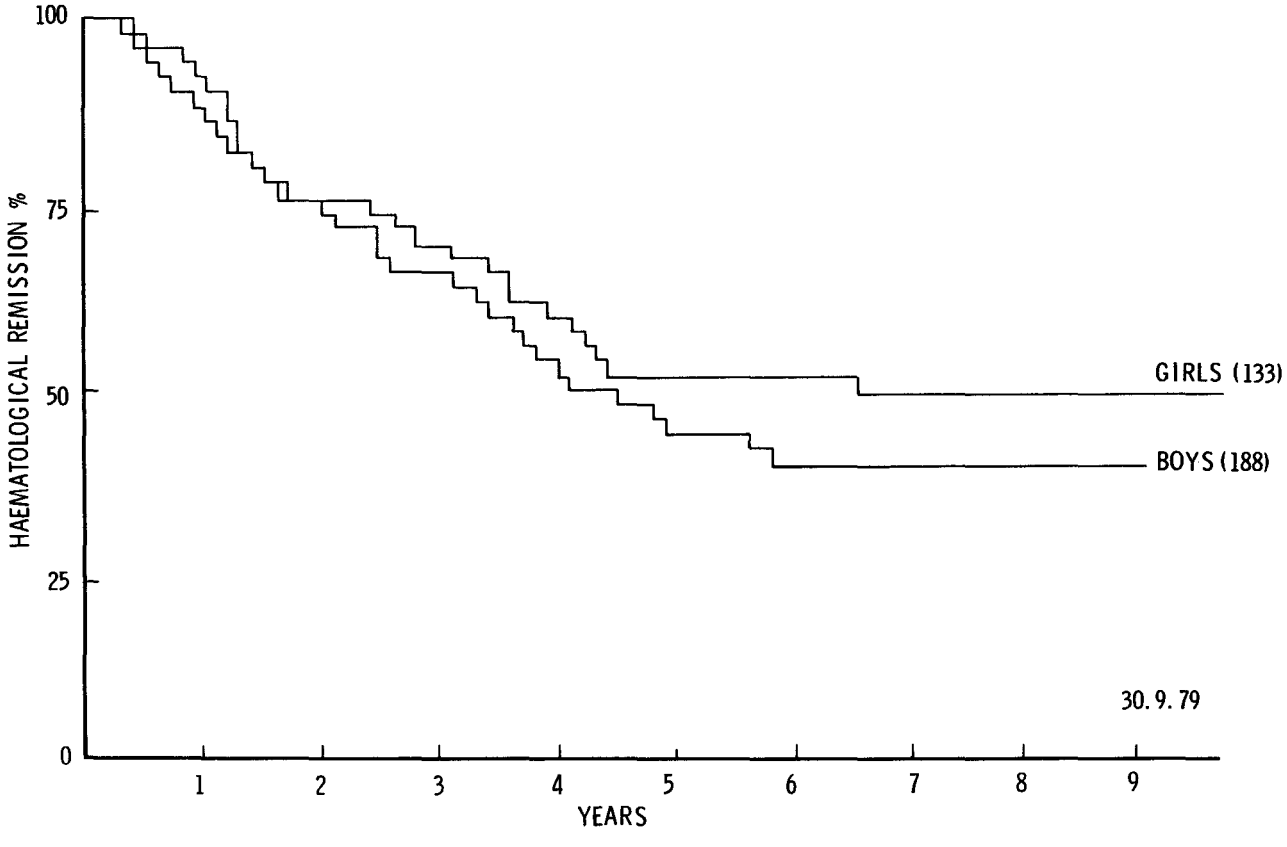


**Fig. 8.** Haematological remission duration in both sexes, 1970–78. Note similar but less marked divergence

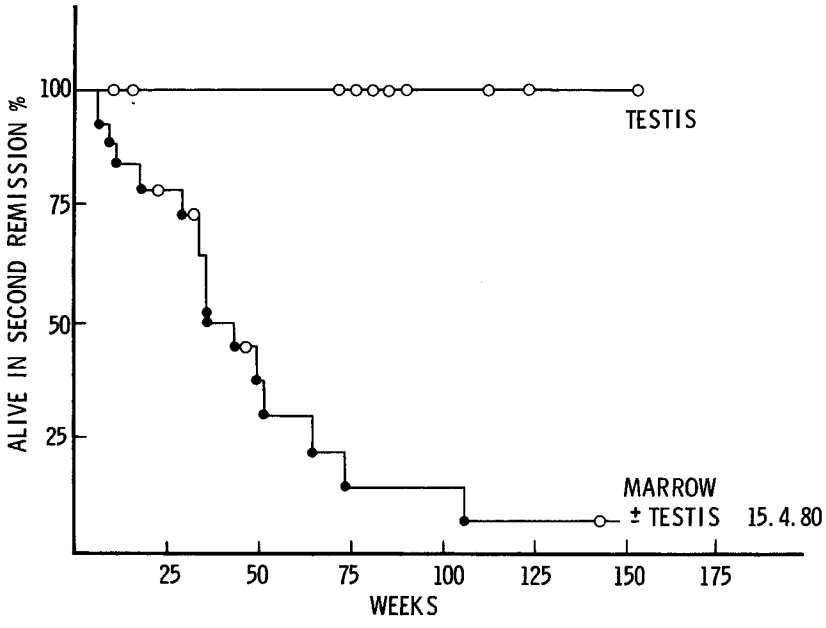


**Fig. 9.** Comparison of duration of second remission in boys with isolated testicular infiltration at or after stopping chemotherapy and boys with marrow relapse with or without testicular involvement. *Open circles* denote patients still in remission

quently developed testicular leukaemia. Boys with overt or occult infiltration are treated with radiotherapy to both testicles (2400 rads) a course of intrathecal methotrexate injections and 2 years of continuous chemotherapy. Preliminary results in ten boys thus treated are encouraging and show that at least in the short term isolated testicular relapse has a better prognosis than bone marrow relapse (Fig. 9).

## D. Conclusions

The two major areas of concern are deaths during continuing (maintenance) treatment and bone marrow relapse. The duration of haematological remission in the series of UKALL trials has not been improved by a variety of manipulations of continuing treatment. It is to be hoped that early intensification of treatment will increase the proportion of patients achieving long-term haematological remission and improve the poor prognosis for boys hitherto observed in the UKALL trials.

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