A descriptive study of randomised trials of treatments for childhood acute lymphoblastic leukaemia

RUNNING TITLE

Randomised trials in childhood leukaemia

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SUMMARY

This report presents a historical and descriptive account of randomised trials in childhood leukaemia since the earliest such studies in the 1960s. It focuses on trials that began before 1988 making use of the register of trials developed for a systematic review of treatments for acute lymphoblastic leukaemia in children. The number of randomised trials starting each year has increased from one or two in the 1960s to an annual average of five or six in the 1980s. However trials remained relatively small, with more than half of all randomisations accruing less than 200 patients, and only five having more than 1000. Most trials were published more than once.

KEYWORDS

childhood leukaemia, systematic review, randomised trials

INTRODUCTION

During the 1950s randomised trials became increasingly common as a way to assess treatments for many health conditions. However, leukaemia was not one of these. It was, at that time, a fatal disease. The general policy was to use any treatment that might prolong survival.

However, attitudes were changing. A 1963 paper by the Medical Research Council Working Party on comparing high and low dose steroids in the treatment of leukaemia in adults stated that *'current forms of treatment* (for leukaemia) *were in need of critical appraisal'* and that *'the* (1957 Steering) *Committee recommended that six Working parties should be formed, and that one of them should examine the possibilities of carrying out therapeutic trials in leukaemia'* MRC (1963).

Through the 1960s, survival rates in childhood acute lymphoblastic leukaemia gradually improved. By 1971 investigators at the St Jude hospital in Memphis concluded '*Childhood lymphocytic leukaemia can no longer be considered an incurable disease. Palliation is no longer a justifiable approach to its initial treatment'* Pinkel *et al* (1971). Randomised trials were needed to distinguish between treatments with moderate differences in their effects on survival or disease-free survival.

In the early years of the 21st century, children with acute lymphoblastic leukaemia have a good chance of cure. Randomised trials are now not only used to investigate survival and disease-free survival differences between treatments but also to investigate differences in

their late effects and toxicity. Randomised trials now need to be larger than before, in order to detect smaller differences in outcomes between increasingly complex treatment regimens.

However, individual randomised trials are still rarely big enough to provide reliable evidence on some important outcomes on their own. Sufficiently large-scale randomised evidence might only be possible through systematic reviews. For these to be valid as high a proportion of relevant trials as possible must be included Clarke and Stewart (1994), and this report is based on the trials that have been identified for a systematic review of treatments for childhood acute lymphoblastic leukaemia.

CURRENT PROJECT

Trial identification can be the most difficult and time-consuming part of systematic reviews. It needs to overcome recognised biases, which mean that some trials will be published quickly and more than once, while others may never reach publication.
The Cancer Overviews Group at the Clinical Trial Service Unit, University of Oxford has considerable experience in the identification of randomised trials EBCTCG (1990). In the early 1990s it began a collaborative overview of individual patient data from randomised trials of any treatment of childhood leukaemia Childhood ALL Collaborative Group (1996).

The methods used for trial identification included computer aided literature searches (on-line and using CD-ROM); hand-searching of journals and of abstract books from major

meetings; and contacting known trialists who might have conducted, or know of, further trials.

A register of randomised trials, which began before 1 January 1988 and which were therefore eligible for the collaborative overview, and of reports of these that had been published before 1 January 2000, was compiled.

RESULTS

A total of 149 randomised trials and 257 reports of these have been identified (some of which reported more than one trial or randomisation). The 149 trials include a total of 243 separate randomisations, since some trials involved more than one randomisation (for example, for induction and maintenance treatments). Ninety (60%) trials contained one randomisation, 35 trials contained two, 19 trials three, two trials contained 4 and 5 and one contained ten randomisations. Of the 257 reports, 195 were journal articles, 51 meeting abstracts and 11 book chapters.

In many of the analyses presented here it will be the **randomisation** rather than the **trial** which is the object of interest. For example, a trial may consist of two randomisations, each addressing a completely separate treatment question; the first between two induction treatments and the second between two different lengths of maintenance treatment. Throughout this report the terms ‘trial’ and ‘randomisation’ will be used in this sense.

Number of patients

Data on the number of randomised patients were available for 212 of the 243 randomisations (Fig 1). The median number of patients accrued was 126. 134 of the 212 randomisations (63%) accrued less than 200 patients. Of these, 41 (19% of the 212) accrued fewer than 50 patients. Five randomisations included more than 1000 patients. The randomisation with the most patients was the CCG-105 trial, which randomised 1606 children into four arms: Intensified induction and consolidation, delayed intensification, both or neither. (The trial also contained a two-way randomisation between cranial irradiation and methotrexate.) Tubergen *et al* (1993).

Geographic location

Data are available on whether a trial is single- or multi-centre for 147 of the 149 trials. Of these 123 (84%) are multi-centre and 24 single centre.

Information is available on whether a trial took place in one country or was international for 129 of the 149 trials. Of these 129, 82 (64%) were single-country trials and 40 (31%) involved a few adjacent countries. For example those run by the BFM Children's Group (based in Germany) involved West Germany and Austria and trials coordinated by GATLA included Argentina, Brazil, Cuba and Uruguay. Only 7 trials (5%) recruited patients in different continents. For example, the USA Cancer and Leukemia Group B (CALGB) has run trials collaborating with Switzerland, Finland and South Africa.

Date of start of trial

As mentioned above, trials beginning in or after 1988 were excluded from the list that forms the basis of this report. Data on the date the trial started are available for 139 of the 149 trials (Fig 2). The earliest randomised trial in childhood acute lymphoblastic leukaemia identified began in 1962. This was an immunotherapy trial run by the French Institut de Cancerologie et d'Immunogenetique (INSERM) Mathe *et al* (1977). There has been a steady increase in the number of new trials starting since then. 1979 appears to have been a particularly productive year, with 18 of the 139 (13%) trials for which the start date is known, beginning then. The five randomisations with the largest number of patients began in 1978, 1981, 1983 (twice) and 1985.

Duration of accrual period

Data are available on the length of time that the randomisation was open for 219 of the 243 randomisations (Table I). The median length of this period was 2 years and 7 months. 18 of the 219 randomisations (8%) were open for more than 5 years.

Method of randomisation

This was rarely reported in these trials in childhood leukaemia, as has been found in studies in other areas of health care Juni *et al* (2001). Out of these 243 randomisations, information on the method of randomisation was available in the reports for only 47. Of these, six randomisations were done via a central computer, 24 via notification to a central office and 17 using sealed envelopes in the individual centres.

Frequency of publication

Table II shows the distribution of frequency of publication for the randomisations. Publications have not been found for 26 (11%). Most randomisations have been published more than once, although the most frequent number of publications per randomisation is one (84 (35%) of 243 randomisations). The five randomisations with the largest number of patients were published three, four, five and six (twice) times.

The most frequently published randomisation (13 reportings) was SJCRH X, a single randomisation equivalence trial, conducted by the St Jude Children's Research Hospital in Memphis, USA Abromowitch *et al* (1988a, b), Bowman *et al* (1984), Mulhern *et al* (1991), Ochs *et al* (1983), Ochs *et al* (1986), Ochs *et al* (1989), Ochs *et al* (1991), Pui *et al* (1985), Pui *et al* (1989), Pui *et al* (1991), Pui *et al* (1992), Williams *et al* (1991). This was a randomisation between two first-line consolidation and maintenance treatments. The second treatment group included cranial irradiation during consolidation and a more complex maintenance regimen than the first. The trial was open between May 1979 and January 1984, and accrued 309 patients. It was funded with both Government and charity money. The randomisation procedure was done using a central computer and a minimisation of imbalance design. The trial was open to standard risk children and was a single-centre study.

The first report for the trial was published in December 1983 Ochs *et al* (1983) and the first report giving results appeared in March 1984 Bowman *et al* (1984). The thirteenth

reporting was in February 1992 Pui *et al* (1992). All reports were published in the English language. Eight of the articles reported results. Six of these reported on the main questions in the study, by comparing the relapse rates and in particular the CNS relapse rates for the two randomised treatment groups. The other two articles dealt with other outcomes only: one compared the testicular relapse rates for the two groups, and the other the incidence of acute myeloid leukaemia as a secondary disease.

CONCLUSION

This report presents a historical and descriptive account of randomised trials in childhood leukaemia since the earliest such studies in the 1960s. It focuses on trials that began before 1988 in order to make use of the register of trials that was developed for a systematic review of treatments for acute lymphoblastic leukaemia in children. Many randomised trials will have started since then Childhood ALL Collaborative Group (2001), but the comprehensive searching done for this existing register has not yet been done for more recent trials. The number of randomised trials starting each year has increased from one or two in the 1960s to an annual average of five or six in the 1980s. However trials remained relatively small, with more than half of all randomisations accruing less than 200 patients, and only five having more than 1000. Most trials were published more than once, typically in journals. Unfortunately, as has been found with other series of trials, the reporting of the methods of these randomised trials in leukaemia could have been better.

This report forms part of a wider, ongoing project investigating this series of randomised trials. The primary aim of which is to assess the extent of searching needed to produce reliable results in systematic reviews of treatments for childhood leukaemia. This brief report highlights some important factors relating to this: the longevity of randomised trial research in this disease, the fact that most of these trials have been relatively small and conducted within single countries, and that many of them have been published once only.

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REFERENCES

Abromowitch M, Ochs J, Pui C-H, Kalwinsky D, Rivera GK, Fairclough D, Look T, Hustu HO, Murphy SB, Evans WE, Dahl GV, Bowman WP (1988 a) High-dose methotrexate improves clinical outcome in children with acute lymphoblastic leukemia: St Jude total therapy study X. *Medical and Pediatric Oncology* **16(5):** 297-303

Abromowitch M, Ochs J, Pui C-H, Fairclough D, Murphy SB, Rivera GK (1988 b) Efficacy of high-dose methotrexate in childhood acute lymphoblastic leukemia: analysis by contemporary risk classification. *Blood* **71(4):** 886-869

Bowman WP, Ochs J, Pui C-H, Kalwinsky DK, Abromowitch M, Aur RJA, Rivera G, Simone JV (1984) New directions of St Jude total-therapy protocols: Study X for standard-risk childhood acute lymphoblastic leukemia. *Leukemia Research: Advances in Cell Biology and Treatment* (eds Murphy SB & Gilbert JR) pp 203-211. Elsevier Science Publishing: Oxford

Childhood ALL Collaborative Group (1996) Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. *Lancet* **347:** 1783-1788

Childhood ALL Collaborative Group (2001*) International Register of Current Randomised Trials in Childhood Acute Lymphoblastic Leukaemia*. Clinical Trial Service Unit: Oxford

Clarke MJ, Stewart LA (1994) Obtaining data from randomised controlled trials: how much do we need to perform reliable and informative meta-analyses? *British Medical Journal* **309:**1007-1010

Early Breast Cancer Trialists' Collaborative Group (1990) *Treatment of Early Breast Cancer. Volume 1. Worldwide Evidence 1985-1990.* Oxford University Press: Oxford

Juni P, Altman DG, Egger M (2001) Assessing the quality of randomised trials. *Systematic Reviews in Health Care* (eds Egger M, Davey Smith G, Altman DG) pp 87-108 British Medical Journal Publications: London

Mathe G, Amiel JL, Schearzenberg L, Schneider M, Cattan A, Schlumberger JR, Hayat M, de Vassal F (1977) Original papers/memoirs: Follow-up of the first (1962) pilot study on active immunotherapy of acute lymphoid leukaemia: A critical discussion. *Biomedicine* **26:** 29-35

Medical Research Council Working Party (1963) First report to the Medical Research Council of the Working Party on the evaluation of different methods of therapy in leukaemia. Treatment of acute leukaemia in adults: Comparison of steroid therapy at high and low dosage in conjunction with 6-Mercaptopurine. *British Medical Journal* **1**: 7-14

Mulhern RK, Fairclough D, Ochs J (1991) A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy or no cranial irradiation. *Journal of Clinical Oncology* **9(8):** 1348-1356

Ochs JJ, Parvey LS, Whitaker JN, Bowman WP, Ch'ien L, Campbell M, Coburn T (1983) Serial cranial computed-tomography scans in children with leukemia given two different forms of central nervous system therapy. *Journal of Clinical Oncology* **1(12):** 793-798

Ochs J, Parvey LS, Mulhern R (1986) Prospective study of central nervous system changes in children with acute lymphoblastic leukemia receiving two different methods of central nervous system prophylaxis. *Neurotoxicity* **7(2):** 217-226

Ochs J, Mulhern R, Fairclough D, Parvey L, Ch'ien L, Mauer A, Simone J (1989) Prospective evaluation of central nervous system (CNS) changes in children with acute lymphoblastic leukemia (ALL) treated with prophylactic cranial irradiation (RT) or IV methotrexate (MTX). *Proceedings of the Annual Meeting of the American Society of Clinical Oncology* **8:** 212 (a824)

Ochs J, Mulhern R, Fairclough D, Parvey L, Whitaker J, Ch'ien L, Mauer A, Simone J (1991) Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate. A prospective study. *Journal of Clinical Oncology* **9(1):** 145-151

Pinkel D, Hernandez K, Borella L, Holton C, Aur R, Samoy G, Pratt C (1971) Drug dosage and remission duration in childhood lymphocytic leukemia. *Cancer* **27:** 247-256

Pui C-H, Dahl GV, Bowman WP, Rao BN, Abromowitch M, Ochs J, Rivera G (1985) Elective testicular biopsy during chemotherapy for childhood leukemia is of no clinical value. *Lancet* **2:** 410-412

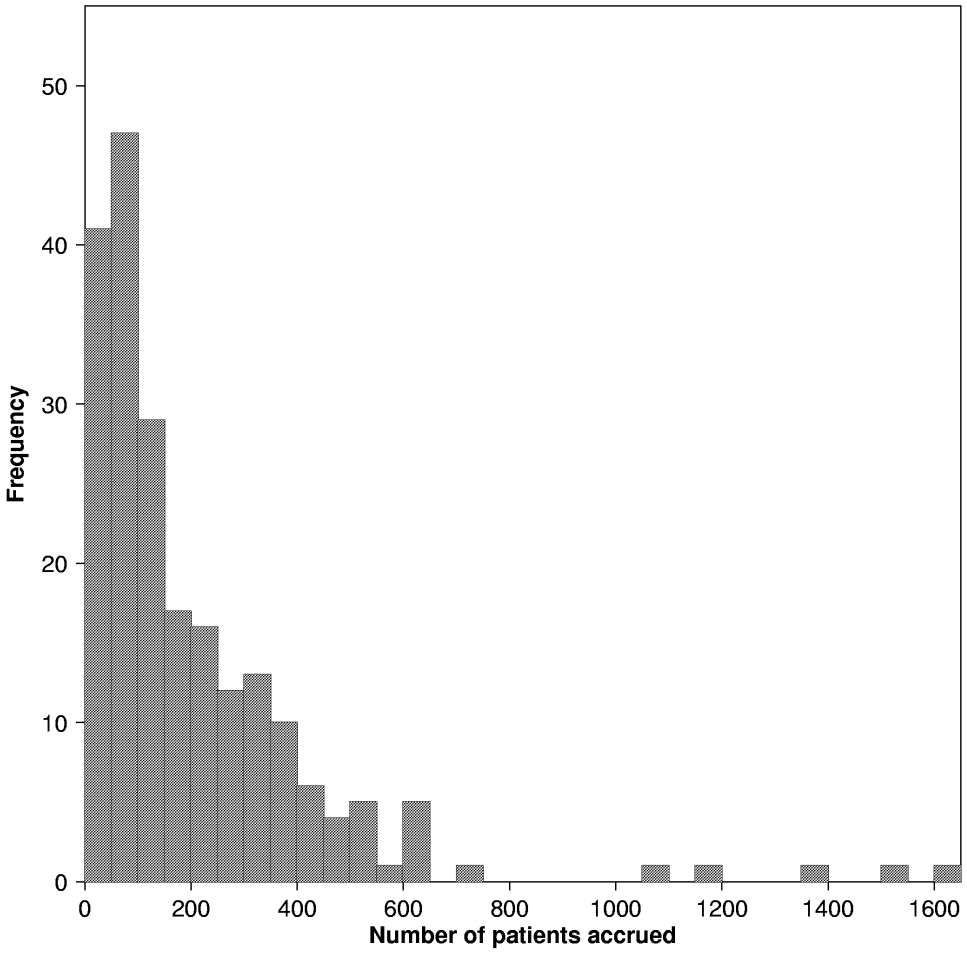
Pui C-H, Behm FG, Raimondi SC, Dodge RK, George SL, Rivera GK, Mirro J, Kalwinsky DK, Dahl GV, Murphy SB, Crist WM, Williams DL (1989) Secondary acute myeloid leukemia in children treated for acute lymphoblastic leukemia. *New England Journal of Medicine* **321(3):** 136-142

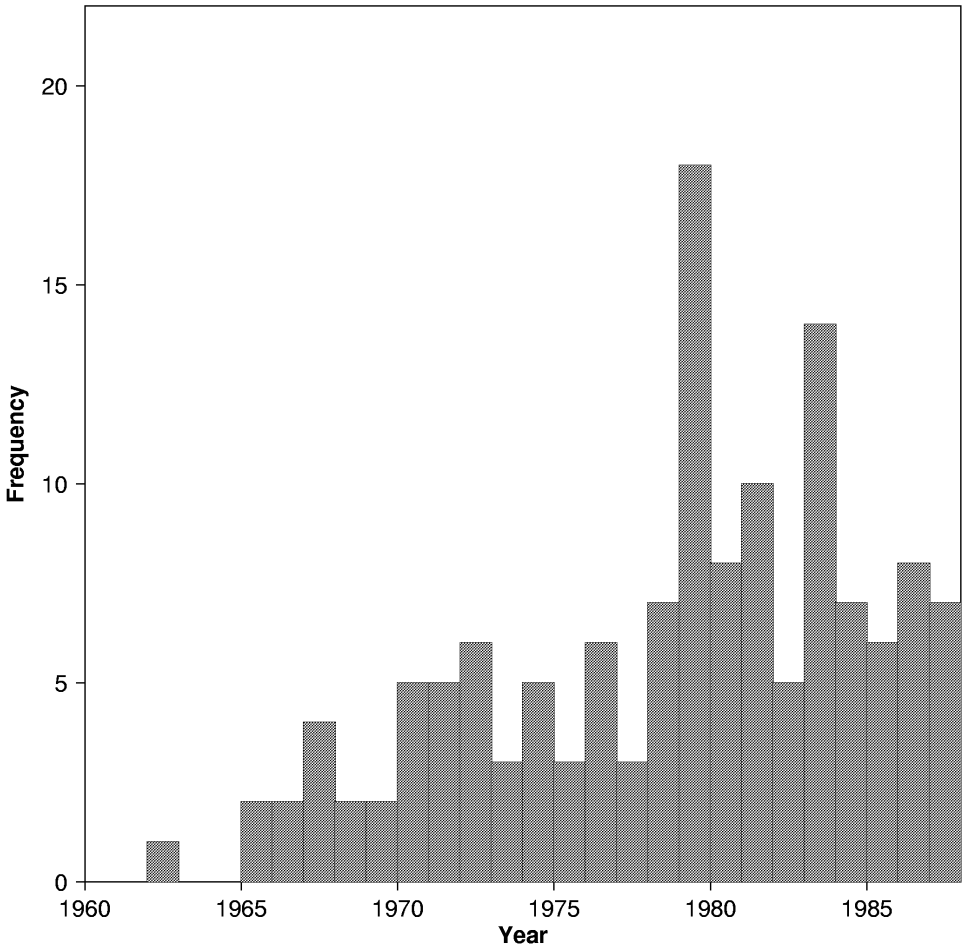
Pui C-H, Ribeiro RC, Hancock ML, Rivera GK, Evans WE, Raimondi SC, Head DR, Behm FG, Mahmoud MH, Sandlund JT, Crist WM (1991) Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *New England Journal of Medicine* **325(24):** 1682-1687

Pui C-H, Simone JV, Hancock ML, Evans WE, Williams DL, Bowman WP, Dahl GV, Dodge RK, Ochs J, Abromowitch M, Rivera GK (1992) Impact of three methods of treatment intensification on acute lymphoblastic leukemia in children: Long-term results of St Jude total therapy study X. *Leukemia* **6(2):** 150-157

Tubergen GD, Gilchrist GS, O'Brien RT, Cocchia PF, Sather HN, Waskerwitz MJ, Hammond GD (1993) Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: A Children's Cancer Group phase III study. *Journal of Clinical Oncology* **11(3):** 527-537

Williams KS, Ochs J, Williams JM, Mulhern RK (1991). Parental report of everyday cognitive abilities among children treated for acute lymphoblastic leukemia. *Journal of Pediatric Psychology* **16(1):** 13-26


Frequency
50
40
30
20
10
0
0
200
400
600
800
1000
1200
1400
1600
Number of patients accrued


20
15
10
5
0
Frequency
1960
1965
1970
1975
1980
1985
Year

Duration of randomisation period (years)	Frequency
0-1	31
1-2	47
2-3	51
3-4	43
4-5	29
5-6	10
6-7	5
7-8	2
8-9	1
Total	**219**

Number of times published	Frequency
0	26
1	84
2	42
3	23
4	24
5	15
6	12
7	12
8	3
9	1
13	1
Total	**243**

Fig 1. Randomisations: number of patients accrued

31 randomisations do not contribute to the figure because the number of patients accrued is currently not available.

Fig 2. Trials: year started

10 randomised trials do not contribute to the figure because the year they started is currently not available.

Table I. Randomisations: duration of recruitment period

24 randomisations are not represented in the table because one or both of their start and close date are currently not available.

Table II. Randomisations: number of publications