Published in final edited form as:
*Leukemia*. 2011 June ; 25(6): 953–959. doi:10.1038/leu.2011.37.

# Meta-analysis of randomized trials comparing thiopurines in childhood acute lymphoblastic leukaemia

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## Abstract

Mercaptopurine has been used in continuing treatment for childhood acute lymphoblastic leukaemia since the mid 1950s. Recent advances in the understanding of thiopurine pharmacology indicated thioguanine might be more effective than mercaptopurine. The US and UK cooperative groups began randomized thiopurine trials and agreed prospectively to a meta-analysis. All randomized trials of thioguanine versus mercaptopurine were sought and data on individual patients were analysed by standard methods. Combining three trials (from US, UK and Germany), the overall event free survival (EFS) was not significantly improved with thioguanine (Odds ratio (OR) = 0.89; 95% confidence interval 0·78–1·03). Apparent differences in results between trials may be partly explained by the different types of patients studied. The larger treatment effect reported in males in the US trial was confirmed in the other trials. There was heterogeneity between sex/age subgroups (p=0·001), with significant EFS benefit of thioguanine only seen for males aged under 10 years old (OR=0·70; 0·58–0·84), although this did not result in a significant difference in overall survival (OR=0·83; 0·62–1·10). Additional toxicity occurs with thioguanine. Mercaptopurine remains the standard thiopurine of choice, but further study of thioguanine may be warranted to determine whether it may benefit particular subgroups.

### Keywords

Thiopurine; mercaptopurine; thioguanine; leukaemia; childhood; systematic review

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**Conflict of interest**
The authors declare no conflict of interest.


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## Introduction

It has long been recognised that thiopurines are critical components in the treatment for acute lymphoblastic leukaemia (ALL). In childhood ALL mercaptopurine (MP) has usually been used in daily long term maintenance therapy, with thioguanine (TG) limited to intensification blocks. Research since the 1980s on the metabolism of the two drugs has suggested theoretical reasons why thioguanine might be more effective. Therefore, in the 1990s trials were initiated to compare the clinical effectiveness of the two thiopurines.

A worldwide collaboration of trialists had previously been formed, whose aim was to perform meta-analyses of randomised trials using individual patient data on the most important current questions. At the start of the US Childhood Cancer Group (CCG) and UK Medical Research Council (MRC) randomized trials comparing thioguanine and mercaptopurine, it was agreed prospectively that when complete the trials would be combined in a meta-analysis. Searches of MEDLINE, EMBASE and clinical trial databases, meeting abstracts, review articles and reference lists found an additional trial addressing the same thiopurine question and this study was included in order to perform a comprehensive meta-analysis.

The COALL-05-92 trial reported its results first[1] and found no evidence of benefit for TG over MP, with similar EFS in the two treatment arms. Furthermore, the use of TG was complicated by prolonged myelosuppression with marked thrombocytopenia. However, a small, but clinically worthwhile, benefit could not be ruled out as fewer than 500 patients were randomised and no major side effects were seen. The report of MRC ALL97[2] concluded that TG caused excess toxicity without an overall benefit. A reduction in the risk of CNS relapse was offset by an increased risk of death in remission and there was evidence of greatly increased hepatic toxicity with thioguanine. In contrast, the CCG-1952 trial reported as an abstract in 2002[3] that EFS was significantly better with thioguanine by 8% at 5 years. However, as in the UK trial, TG-induced veno-occlusive disease of the liver forced many patients to switch from TG to MP. During the course of this trial the dose of TG was reduced from 60mg/m$^2$ to 50mg/m$^2$, and the greatest difference in EFS between TG and MP was seen for boys who began at 60mg/m$^2$. The recent publication of CCG-1952[4] confirmed a 5% better EFS at 7 years, due to decreased bone marrow and isolated CNS relapses, but no increase in overall survival.

## Materials and methods

Data were received on each patient randomized between MP and TG in the COALL-05-92, CCG-1952 and MRC ALL97 trials. They were checked for internal consistency, balance between treatment groups by initial features, randomization dates and length of follow-up, and consistency with publications. Queries were sorted out by correspondence with the trialists, who were also sent summary tabulations to check that the data had been correctly interpreted.

Analyses were of time from randomisation to event within trial, with the observed minus expected (O-E) number of events and its variance, obtained by the log-rank method, added over the three trials, used to calculate an overall odds ratio (OR) and its 95% confidence interval (CI). Descriptive curves were drawn using these statistics[5]. Outcomes analysed were central nervous system (CNS) relapse, non-CNS relapse, secondary tumour, death without remission, and death in remission. For each of these outcomes, only the first event was counted for each patient, censoring at other event types. Event free survival, including all these event types, was the primary outcome measure, and overall survival was also analysed.

Heterogeneity between trials was tested using chi-square statistics and the $I^2$ measure of consistency.[6]

Subgroup analyses pre-specified were by gender, age group (<10, ≥10), white blood count (WBC) (<10, 10–19, 20–49, 50–99, ≥100) and immunophenotype (B-lineage, T-lineage). In the reported analyses, the two highest WBC groups were combined because the numbers were small.

## Results

Table 1 shows the recruitment period, main eligibility criteria and treatment comparison for the three trials. The COALL and MRC trials included all ALL risk groups, while CCG-1952 was only for NCI standard risk children (age < 10 years and WBC<$50\times10^9$/l).

The COALL-05-92 treatment regimen consisted of a 7-day pre-phase with daunorubicin and intrathecal (IT) methotrexate (MTX), induction with vincristine, daunorubicin and methylprednisolone, intensification, CNS prophylaxis, re-induction and maintenance to 2 years. Children aged ≥10 years, with WBC≥$25\times10^9$/l or T or pre-pre-B-ALL were considered high risk and had two additional treatment blocks in intensification and longer re-induction. CNS prophylaxis consisted of IT MTX (18 doses given overall, with 4 during the phase defined as CNS prophylaxis and 6 during maintenance). 12Gy cranial irradiation was given to HR children with WBC≥$25\times10^9$/l or T-ALL (from April 1994 this was changed to WBC≥$50\times10^9$/l or T-ALL), and 18Gy to those with CNS disease. Re-induction and maintenance IT doses were omitted in patients who received cranial irradiation so that they received only 9 doses of IT MTX overall.

The CCG-1952 treatment consisted of induction with IT cytarabine, vincristine, asparaginase, prednisone and IT MTX, consolidation, interim maintenance, 2 intensification blocks and maintenance to 2·25 years for girls and 3·25 years for boys. Only rapid early responders (≤25% blasts at day 15) were randomized for thiopurine. Patients were additionally randomized, in a factorial design, between IT MTX and triple IT therapy (MTX, cytarabine, hydrocortisone sodium succinate), with all patients receiving 2 doses of IT MTX in induction plus 17 doses (girls) or 21 doses (boys) of IT MTX or triple IT overall according to the randomized allocation. Craniospinal irradiation (24 Gy cranial, 0·6 Gy spinal) was administered to those with CNS disease at diagnosis during the consolidation phase.

MRC ALL97 included a randomization between the steroids prednisolone and dexamethasone. Treatment consisted of induction with vincristine, allocated steroid, asparaginase, IT MTX, 2 short intensification blocks with CNS-prophylaxis in between, interim maintenance, further intensification and maintenance to 2 years. CNS prophylaxis consisted of a total of 16 doses of IT MTX for those with WBC<$50\times10^9$/l, or 3 doses of high dose MTX (6 or 8 g/$m^2$) plus 16 doses of IT MTX or 24Gy cranial irradiation plus 9 doses of IT MTX for WBC ≥$50\times10^9$/l (randomized). In November 1999 there was a major revision. From this time, the treatment for standard risk children with rapid early response was similar to CCG-1952, apart from the randomization of the steroid. High risk children received daunorubicin additionally in induction and more intensive consolidation. All children classified as slow early responders during induction (>25 % blasts at day 15 if standard risk, or at day 8 if high risk) were switched to a more intensive regimen with augmented consolidation and more vincristine, oral MTX and PEG asparaginase during the interim maintenance periods. Girls were treated for 2 and boys for 3 years. Girls received 19 or 22 doses of IT MTX overall, and boys received 23 or 26 doses, with those who were high risk initially or slow early responders, receiving the additional doses.

The total number of children randomized to TG or MP was 4000. Follow-up continues beyond publication in some trials. With the maximum follow-up year of 2005 in COALL-05-92, 2005 in CCG-1952 and 2008 in MRC ALL97, median follow-up of all patients alive or lost to follow-up was 8.9 years, 6.4 years and 8.9 years, respectively. Patient numbers by initial characteristics in each trial are shown in table 2. Trials had similar proportions of males and children with B-lineage disease. There were somewhat more children classified as having T-cell ALL in COALL-05-92. The main difference between the trial populations was due to the inclusion of only NCI standard risk patients in the CCG-1952 trial, so that there were no children aged 10 years or over at diagnosis, compared with 21% in COALL-50-92 and 15% in MRC ALL97, and none with WBC≥$50\times10^9$/l, compared with 21% in COALL-50-92 and 18% in MRC ALL97.

There was a suggestion that the relative effect of TG might differ between trials (Figure 1a; heterogeneity test p=0·04, $I^2$ = 68%). Significant heterogeneity (p=0·02) was seen for isolated CNS relapse, with an increase in those allocated TG in COALL-05-92 (8 v 2) and decrease in the other trials (33 v 56; 17 v 34), but this may be a chance effect due to small numbers and multiple testing. The difference between trials was not seen for any other individual outcome. CCG-1952 included only standard risk patients and if high risk patients from the other trials were excluded, the heterogeneity between the three trials was no longer seen (Figure 1b; $I^2$=0·0).

Overall there was a small, non-statistically significant, reduction in the event rate with TG (OR=0·89, 95% CI=0·78–1·03, p=0·10). There was a reduction in the CNS relapse rate with TG (OR = 0·74, 95% CI = 0·58–0·95; p=0·02). Thiopurine treatments were balanced between intrathecal therapies in CCG-1952 and between steroid type in MRC ALL97 and there was no evidence of a different effect of TG on CNS relapse between these treatment groups. The reduction in CNS relapse was offset by an increase in the rate of death in first remission in the MRC trial (OR = 1·67, 95% CI = 1·00–2·78, p=0·05, table 3). In the latter trial, those receiving dexamethasone pulses were at increased risk of death in first remission (TG 20/354; MP 5/353; OR = 3·36; 99% CI = 1·02–9·43) compared with those receiving prednisolone (TG 5/396; MP 7/395; OR = 0·73; 99% CI = 0·16–3·17; p for heterogeneity = 0·03). Exclusion of dexamethasone treated patients further reduced the apparent difference in the NCI standard risk group between MRC ALL97 and the other trials and increased the estimated event rate reduction to OR=0·84, 95% CI = 0·72–0·98; p=0·02. There were fewer non-CNS relapses and more secondary tumours (OR=1.87, 95% CI = 0.87-4.04; p=0.11) with TG compared to MP, but not statistically significantly. There was no evidence that secondary tumours (which included several AML, MDS, NHL, Hodgkins disease, and malignant cancers of the bone, brain, thyroid and epithelium) were related to the use of cranial irradiation (XRT). None of the 9 cases in CCG-1952 or 9 cases in MRC ALL97 received XRT; in COALL-05-92 there were 5 cases out of 153 allocated to XRT and 3/320 in the remainder (p=0·07). Six patients died without remission and these are included in the overall event rates, but not analysed separately in further analyses.

The absolute reduction with TG in the proportion with CNS relapse at 5 years was 1·8%, and this resulted in a non-significant reduction of 2·5% in the proportion with any event at 5 years (Figure 2a). A difference did not start to emerge until after 3 years. There was no significant difference in overall survival (OR = 1·07, 95% CI = 0·89–1·30; p=0·47), with 5-year survival 0·9% higher with MP. In addition to the increased deaths in remission and secondary tumours, patients who relapsed had non-significantly poorer survival from relapse if they were in the TG group.

There was no evidence of a different effect on the overall event rate in subgroups by WBC or immunophenotype (Figure 3). There was a possible difference between the effects in

males and females (heterogeneity p = 0·01). This was due chiefly to a difference in treatment effect on CNS relapses (heterogeneity P = 0·0006) (Table 3), with a halving in the CNS relapse rate with TG for males (OR = 0·52; OR = 0·39–0·72; p=0·0001), but no benefit for females (OR = 1·27; 95% CI = 0·85–1·89; p=0·24). There was no significant difference for non-CNS relapse or deaths in first remission. The estimated absolute difference with TG in EFS at 5 years was 5·4% higher among males and 1·1% lower among females. Due to better salvage of MP treated males who relapsed than those who received TG (analysis of time from relapse to death, gave OR = 1.25; 95% CI = 0.94-1.66 for TG v MP), the EFS benefit did not translate into improved overall survival.

There was a difference between the effects on overall events in younger and older patients, with TG showing benefit for those under 10 years but harm for those aged 10 years or over (Figure 3; p=0·004). TG reduced the non-CNS relapse rate in the group aged under 10 years (Table 3; OR = 0·81; 95% CI = 0·66–0·98; p=0·03) but not in those aged 10 years or over (OR = 1·44; 95% CI = 0·89–2·33; p=0·14). There was no difference in overall survival by treatment for younger patients, and better survival with MP for the older ones, again due to improved survival post relapse (heterogeneity p = 0·006). Differences in the effects on other outcomes were not significantly different between age groups, but the overall numbers in the older group are small, so that power to detect differences is low.

The heterogeneity of treatment effect on EFS between age groups and between males and females was confirmed by analysis of the COALL and MRC trials, excluding the CCG trial.

The effect estimates for the four groups by age and sex are shown in table 3 and figure 3. There is a clear reduction in overall event rate with TG for males aged under 10 years (OR = 0·70; 95% CI = 0·58–0·84; or OR = 0·66; 95% CI = 0·54–0·82 excluding dexamethasone treated patients). The effect in this latter group was a reduction of about a quarter in the annual event rate in each of the first 5 years, resulting in an absolute benefit of 6·8% at 5 years (Figure 2b). However, survival was not improved (OR = 0·83, 95% CI = 0·62–1·10).

Toxicity was a major issue in the CCG-1952 and MRC ALL97 trials, which included vincristine/steroid pulses in maintenance, but apparently not in COALL-05-92, without pulses. In MRC ALL97 82 patients randomised to TG developed veno-occlusive disease (VOD) – 68 during maintenance and 14 in intensification, while the twelve who developed this in the MP arm did so during intensification courses which contained TG.[2] One of these patients died of adenovirus infection and one patient required a liver transplant. In CCG-1952 20% of patients randomised to TG developed VOD – 182 during maintenance and 24 in intensification, while the three in the MP arm again developed it after receiving TG in delayed intensification.[4] No deaths occurred but one patient required a liver transplant. In both trials, patients with these problems were switched to MP (82 cases in MRC ALL97 and 262 in CCG-1952). 5% of patients on TG in CCG-1952 developed disproportionate thrombocytopenia (DT) and the incidence of VOD or DT was 28.5% with the higher, and 23% with the lower, starting dose. These problems were not reported in COALL-05-92 although there were more treatment interruptions in the TG group, with a 7·5 fold higher incidence of thrombocytopenia $<100 \times 10^9$/l without leukocytopenia $<1 \times 10^9$/l. On 10 occasions platelet transfusions were given. The estimated increase in VOD between randomised treatments was seven-fold (OR = 7.16, 95% CI = 5.66-9.06).

## Discussion

With the complex treatments used for childhood ALL there are many protocol features which can vary between trials. In these trials comparing thiopurines there are differences in TG doses, and in the timing and type of maintenance treatment. This meta-analysis has

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revealed important clues about the apparent differences in results between trials, which may be at least partly due to the different patients included. By using individual patient data it has been possible to examine treatment effects within subgroups of patients, and to look at specific outcomes separately. The different effects in males and females seen in CCG-1952 were confirmed using data from the other two trials. In addition, high risk patients were included in these trials, allowing examination of effects in older patients not included in the CCG trial.

Possible heterogeneity of effect between males and females, and between younger and older patients suggests that TG improves EFS for males aged <10 years, the largest of the four sex/age subgroups. The event rate was reduced by 30% resulting in an absolute difference of 6·8% at 5 years. Although the point estimates in other groups are in favour of MP, confidence intervals are wide, and whether there is benefit or harm in these groups is unclear. On average, boys received a longer duration of treatment than girls, and this might partly explain the difference. Another reason might be differences in the way boys and girls handle the two drugs.[7,8]

Although differences were not generally statistically significant, deaths in remission and secondary tumours were more frequent with TG in all subgroups, so the treatment effect on relapse rate needs to be large enough to counteract this in order to show EFS benefit.

Since salvage treatment seemed to be more successful for relapses after MP, survival benefit was not seen overall, or for any subgroup. Although TG may be more effective in preventing relapses in some types of patients, its toxicity and lack of effect on survival currently preclude its prolonged use. Ongoing pharmacogenetic studies may yet establish whether there are particular patients who could derive outcome benefit from TG.

## Acknowledgments

The work was funded by a grant from the Kay Kendall Leukaemia Fund (KKL293) with additional support from Cancer Research UK and Medical Research Council. The secretariat for this work was at CTSU, Oxford University (T Elphinstone, V Evans, L Gettins, C Hicks, L MacKinnon, P Morris, S Richards, R Wade, C Wise).

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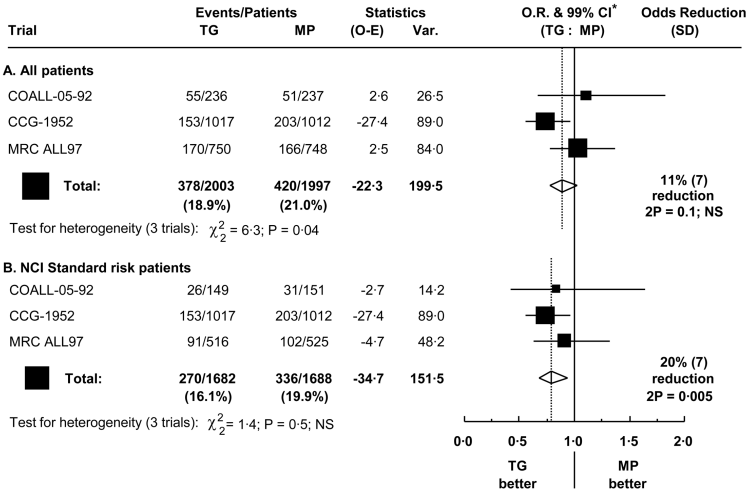


**Figure 1.**

Effect of thiopurine on overall event rate within trials, (a) overall, (b) for NCI standard risk patients only.

TG, thioguanine; MP, mercaptopurine; O-E, observed minus expected; Var, variance; O.R., odds ratio; CI, confidence interval ; SD, standard deviation; NS, not significant; 2P, 2-tailed p value. *95% CI for total.




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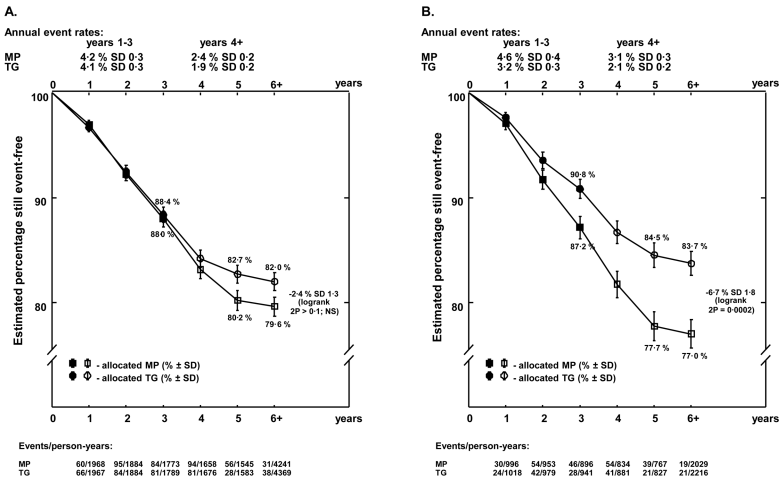


**Figure 2.**

Descriptive event free survival curves showing effect of thiopurine (a) overall (b) within subgroup of males aged under 10 years.

MP, mercaptopurine; TG, thioguanine; SD, standard deviation; NS, not significant; 2P, 2-tailed p value.




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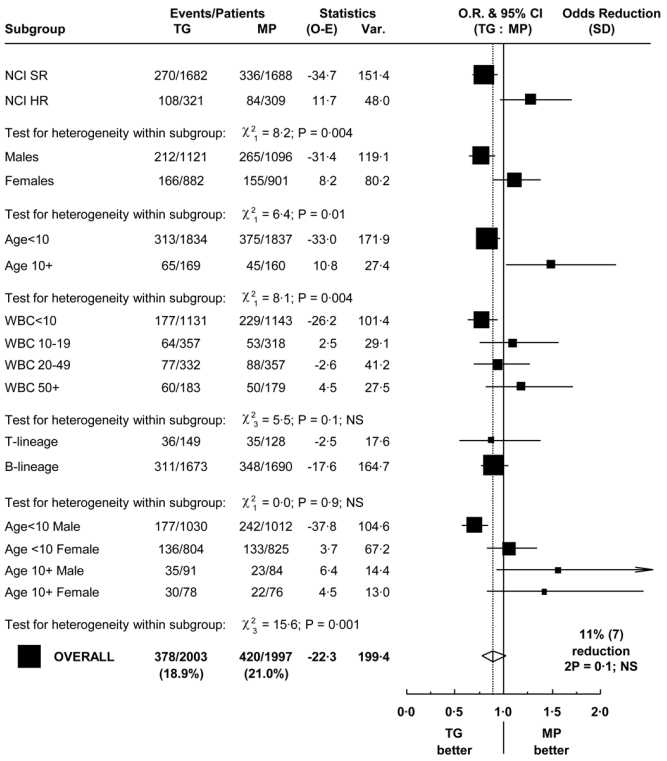


**Figure 3.**

Effect of thiopurine on overall event rate within subgroups.

TG, thioguanine; MP, mercaptopurine; O-E, observed minus expected; Var, variance; O.R., odds ratio; CI, confidence interval ; SD, standard deviation; NS, not significant; 2P, 2-tailed p value.




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## Table 1

Trial descriptions

| Trial | COALL-05-92 | CCG-1952 | MRC ALL97 |
|---|---|---|---|
| Recruitment | 1992–1997 | 1996–2000 | 1997–2002 |
| Main eligibility | Age 1–18 yrs | Age 1–9 yrs & WBC<$50\times10^9$/l | Age 1–18 yrs |
| Thioguanine starting dose | 50 mg/$m^2$ (40mg/$m^2$ if thrombocytopenia a major problem). | 60mg/$m^2$/d to 26 Dec 1997, 50 mg/$m^2$/d thereafter. | 40 mg/$m^2$/d. |
| Dose adjustments | Adjusted to maintain WBC 2–$3\times10^9$/l | Adjusted to maintain neutrophils 1–$2\times10^9$/l and platelets ≥$100\times10^9$/l. | Adjusted to maintain neutrophils ≥$10\times10^9$/l and platelets ≥$100\times10^9$/l, but as low as possible (ALL97) or neutrophils between 0·75–1·5×$10^9$/l and platelets >$75\times10^9$/l (ALL97/99). |
| Thiopurine randomisation phases | Maintenance | Consolidation, interim maintenance & maintenance | Interim & continuing maintenance (ALL97) or consolidation (NCI SR only) & maintenance (ALL97/99) |
| CNS-directed therapies | Continuing i.t. MTX, or i.t. MTX plus 12Gy XRT for WBC≥$25\times10^9$/l (≥50 after April 1994) or T-ALL If CNS disease: 18Gy XRT | Continuing i.t. MTX v triple i.t. therapy (randomised) If CNS disease: 24Gy XRT plus 0·6Gy spinal | Continuing i.t. MTX (ALL97/99), or i.t. MTX plus 24Gy XRT v HDMTX + continuing i.t. MTX (randomised) for WBC≥$50\times10^9$/l (ALL97 only) If CNS disease: i.t. MTX plus 24Gy XRT + continuing i.t. MTX |
| Maintenance vincristine + steroid pulses | None | Vincristine + prednisolone | Vincristine + prednisolone or dexamethasone (randomised) |
| Duration of therapy | 2 years | Girls 2·25 years, boys 3·25 years. | 2 years (ALL97), or girls 2 years, boys 3 years (ALL97/99) |
| Relevant amendments | None | (1) Thioguanine dose (see above) (2) All patient on TG at April 2001 switched to MP | (1) Background treatment modified in 1999. (2) All patients on TG at June 2002 switched to MP |

NCI SR, National Cancer Institute Standard Risk; HDMTX, high dose methotrexate.

i.t. = intrathecal; d=day.

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**Table 2**

Patient characteristics

| Trial | Total[1] | Gender | | Age (years) | | WBC (×10$^9$/l) | | | | Immunophenotype | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | 1-9 | ≥10 | <10 | 10-19 | 20-49 | ≥50 | B-lineage | T-lineage | Other / Unknown |
| COALL-05-92 | 473 | 272 (58%) | 201 (42%) | 376 (79%) | 97 (21%) | 244 (52%) | 44 (9%) | 87 (18%) | 98 (21%) | 394 (83%) | 69 (15%) | 10 (2%) |
| CCG-1952 | 2029 | 1131 (56%) | 898 (44%) | 2029 (100%) | 0 (0%) | 1266 (62%) | 396 (20%) | 367 (18%) | 0 (0%) | 1646 (81%) | 91 (5%) | 292 (14%) |
| MRC ALL97 | 1498 | 814 (54%) | 684 (46%) | 1266 (85%) | 232 (15%) | 764 (51%) | 235 (16%) | 235 (16%) | 264 (18%) | 1323 (88%) | 117 (8%) | 58 (4%) |

[1] Percentages quoted may not add up to 100% due to rounding

**Table 3**

Effect of thiopurine on different outcomes, overall and within age and sex subgroups.

| Numbers with specified outcomes by randomised treatment allocation | | | | | |
|---|---|---|---|---|---|
| Outcome | TG | MP | Odds ratio (95% CI) | 2p | |
| Patients included | 2003 | 1997 | | | |
| Isolated CNS relapse | 58 | 92 | 0·63 (0·46–0·87) | 0·004 | |
| CNS relapse | 107 | 143 | 0·74 (0·58–0·95) | 0·02 | |
| Non-CNS relapse | 215 | 242 | 0·88 (0·73–1·06) | 0·17 | |
| Secondary tumour | 17 | 9 | 1·87 (0·87–4·04) | 0·11 | |
| Death in first remission | 37 | 22 | 1·67 (1·00–2·78) | 0·05 | |
| Death without remission | 2 | 4 | 0·51 (0.10–2·51) | 0·42 | |
| Any event | 378 | 420 | 0·89 (0·77–1·02) | 0·10 | |
| Any death | 214 | 198 | 1·07 (0·89–1·30) | 0·47 | |
| **Age<10 years** | | | | | |
| Patients included | 1834 | 1837 | | | |
| Isolated CNS relapse | 54 | 85 | 0·63 (0·45–0·87) | 0·006 | |
| CNS relapse | 96 | 130 | 0·73 (0·56–0·94) | 0·02 | |
| Non–CNS relapse | 176 | 214 | 0·81 (0·66–0·98) | 0·03 | |
| Secondary tumour | 12 | 8 | 1·54 (0·64–3·70) | 0·34 | |
| Death in first remission | 27 | 20 | 1·36 (0·77–2·41) | 0·30 | |
| Any event | 313 | 375 | 0·82 (0·71–0·95) | 0·01 | |
| Any death | 164 | 171 | 0·95 (0·77–1·18) | 0·63 | |
| **Age 10+ years** | | | | | p-value <10 v 10+ |
| Patients included | 169 | 160 | | | |
| Isolated CNS relapse | 15 | 11 | 0·73 (0·34–1·57) | 0·42 | 0·69 |
| CNS relapse | 4 | 7 | 0·55 (0·17–1·79) | 0·32 | 0·83 |
| Non-CNS relapse | 39 | 28 | 1·44 (0·89–2·33) | 0·14 | 0·03 |
| Secondary tumour | 5 | 1 | 5·02 (0·99–25·47) | 0·05 | 0·21 |
| Death in first remission | 10 | 2 | 3·66 (1·18–11·35) | 0·02 | 0·13 |
| Any event | 65 | 45 | 1·47 (1·01–2·15) | 0·04 | 0·0045 |
| Any death | 50 | 27 | 1·91 (1·22–3·00) | 0·004 | 0·006 |
| **Males** | | | | | |
| Patients included | 1121 | 1096 | | | |
| Isolated CNS relapse | 35 | 71 | 0·48 (0·33–0·71) | 0·0002 | |
| CNS relapse | 53 | 99 | 0·52 (0·39–0·72) | 0·0001 | |
| Non-CNS relapse | 133 | 144 | 0·89 (0·70–1·12) | 0·31 | |
| Secondary tumour | 6 | 6 | 1·07 (0·34–3·33) | 0·91 | |
| Death in first remission | 19 | 13 | 1·43 (0·72–2·87) | 0·31 | |
| Any event | 212 | 265 | 0·77 (0·64–0·92) | 0·004 | |
| Any death | 115 | 118 | 0·96 (0·74–1·24) | 0·76 | |
| **Females** | | | | | p-value M v F |
| Patients included | 882 | 901 | | | |
| Isolated CNS relapse | 23 | 21 | 1·13 (0·62–2·04) | 0·69 | 0·02 |
| CNS relapse | 54 | 44 | 1·27 (0·85–1·89) | 0·24 | 0·0006 |
| Non-CNS relapse | 82 | 98 | 0·86 (0·65–1·16) | 0·33 | 0·90 |
| Secondary tumour | 11 | 3 | 3·44 (1·20–9·84) | 0·02 | 0·14 |
| Death in first remission | 18 | 9 | 1·98 (0·93–4·20) | 0·08 | 0·54 |
| Any event | 166 | 155 | 1·11 (0·89–1·38) | 0·37 | 0·01 |
| Any death | 99 | 80 | 1·26 (0·94–1·69) | 0·12 | 0·17 |

CNS = central nervous system; 2p, 2-tailed p value; M, male; F, female