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Systematic Review and Meta-analysis of Randomized Trials of Central Nervous System Directed Therapy for Childhood Acute Lymphoblastic Leukaemia

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Abstract

Treatment of the central nervous system (CNS) is an essential therapy component for childhood acute lymphoblastic leukaemia (ALL). Individual patient data from 47 trials addressing 16 CNS treatment comparisons were analyzed. Event-free survival (EFS) was similar for radiotherapy versus IT, and radiotherapy plus IT versus IVMTX plus IT. Triple intrathecal therapy (TIT) gave similar EFS but poorer survival than ITMTX, but additional IVMTX improved both outcomes. One trial resulted in similar EFS and survival with IVMTX plus ITMTX versus TIT alone. Radiotherapy can generally be replaced by IT therapy. TIT should be used with effective systemic therapy such as IVMTX.

Keywords

Leukaemia; Meta-analysis; childhood leukaemia; CNS; triple intrathecal therapy

INTRODUCTION

Pre-symptomatic treatment of the central-nervous-system (CNS) is an indispensable component of the successful therapy of childhood acute lymphoblastic leukaemia (ALL)[1]. Historically, pre-symptomatic cranial or craniospinal irradiation was a standard component of treatment for all patients. As concerns about the long-term consequences of radiation increased[2], irradiation was first limited to the brain, then decreased in dose, and finally largely replaced by effective intrathecal and systemic chemotherapy, but retained for patients with high-risk disease or leukemic blasts identifiable in the cerebrospinal fluid at diagnosis. In some contemporary clinical trials, irradiation has been omitted for all patients[3,4]. To successfully prevent the progression or recurrence of leukaemia in the CNS, optimal systemic and intrathecal therapy is necessary[1]. In 2003, we performed a collaborative meta-analysis of randomized trials addressing issues of pre-symptomatic CNS therapy that initiated accrual prior to 1994[5]. In this study, we update this work, and include additional trials that commenced before 2000 to allow adequate follow-up time.

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CONFLICT OF INTEREST STATEMENT
All members of the writing committee declare there are no conflicts of interest.

METHODS

CNS-directed interventions include cranial or craniospinal irradiation, intrathecal drugs, intravenous methotrexate at a dose of ≥0.5 g/m^2 plus leucovorin, or intravenous mercaptopurine. This paper focuses on newly diagnosed patients and excludes those who received craniospinal irradiation, a strategy no longer in use. Intravenous mercaptopurine will be reported separately.

Other drugs, which also have an effect on CNS control, in particular type of steroid[6-8] will be addressed in a future study, but a summary of steroid use in the current set of trials has been recorded. Thioguanine also appears to influence CNS control, but is not currently in use in most protocols because of concerns about toxicity[9].

Trials were identified following detailed search of electronic databases including MEDLINE and EMBASE. Additional hand-searching of review articles, meeting abstracts, reference lists of published trials, and the content lists of major cancer and general medical journals was undertaken. Members of the Childhood ALL Collaborative Group and other experts were consulted to ensure the completeness of the resulting list of trials. For all trials, ethical committee review and individual/ family informed consent were obtained as per national standard. Data collected on each trial included period of recruitment, eligibility criteria, randomized treatment elements and timing, and any CNS-directed treatment given in addition to the randomized question.

For all trials the following information was sought for each patient aged 21 years or younger at random assignment to treatment: date of diagnosis, age or date of birth, gender, white blood count (WBC) at diagnosis, immunophenotype, date of random assignment to treatment and treatment allocation, site of any first relapse, as well as time of first remission, relapse, death or last contact. In addition, the date and type of any secondary tumour were sought. Data were checked for internal consistency, balance between treatment groups by initial features, randomization dates, and length of follow-up, and consistency with published results.

All first event outcomes were measured from date of randomization. Primary outcomes were event-free survival (EFS) and overall survival (OS). Any induction failure, relapse or death was counted as an adverse event. As many trials did not record secondary tumours, these events were not included in analyses. Secondary outcome measures were no remission (defined as death without remission achievement), isolated CNS relapse, any CNS relapse (isolated CNS relapse plus combined relapses with CNS involvement), non-CNS relapse, and death in remission which included death due to secondary tumour. Relapse data were obtained only for first relapse. Survival from relapse was also analyzed.

Standard statistical meta-analysis methods were used. Within trials, analyses examined time from randomization to any event, with the observed minus expected (o-e) number of events and its variance (v) obtained by the log-rank method. These o-e values were then added over all trials to produce a total (T), with variance (V) equal to the sum of the separate variances. These were used to calculate an overall odds ratio (OR), or ratio of event rates, and its 95% confidence interval (CI) equal to $\exp(T/V \pm 1.96/\sqrt{V})$. Results are presented as forest plots with a square representing the point estimate of the OR and a horizontal line showing the 99% confidence interval for each trial. The size of the square is proportional to the number of events, not patients. Overall estimates are shown by a diamond with the width representing the 95% confidence interval. All p-values given are two-sided. Heterogeneity between the effects in different trials or subgroups was tested with X^2_{n-1} equal to $S\text{-}T^2/V$, where S is the sum of $(o\text{-}e)^2/v$ from each of n trials or n subgroups[10].

T and V obtained by summing o-e and v from log rank analyses restricted to each one year time period were used to estimate the log OR, b, for each year. The estimated overall event rate in each time period, r, equals the number of events divided by the number of person years, and the probability of surviving event-free during that year is p=exp(-r). Descriptive survival curves were drawn from the separate probability estimates p+0.5p(p-1)b for one treatment group, and p-0.5p(p-1)b for the other treatment group[10].

Trials were categorized *a priori* and the results combined according to the treatment comparisons and background CNS-directed treatments. We examined conventional pre-specified subgroups by gender, age group (<10, ≥10 years), WBC (<10, 10-19, 20-49, 50-99, ≥100 × 10^9/L) and immunophenotype (B-lineage, T-lineage).

RESULTS

Data were available for 47 trials, ten of which were not included in the previous analyses. 45 trials had a median follow-up of at least five years. Studies were grouped into 11 categories by randomized comparison. Table I gives details of the CNS-directed treatments[11-56]. Steroid use is given in supplementary table S1. Supplementary tables S2 and S3 show the distribution of patient and disease characteristics and median follow-up for each trial.

Grouping of trials

A. *Triple intrathecal therapy (TIT) with methotrexate, hydrocortisone and cytarabine versus intrathecal (IT) methotrexate (IT MTX) therapy*. One new trial, involving 2029 NCI standard-risk (age<10 years and WBC<50 × 10^9/L) patients, addressed this question.

B. *Radiotherapy plus IT therapy versus extra IT therapy*. Nine trials, including one new trial, addressed this question. Data were available for eight of these trials, involving 2995 patients, which compared treatment regimens with either 18 or 24 Gy cranial irradiation (CRT) plus some IT treatment with the same regimen without CRT but with additional doses of IT MTX or TIT, the use of double IT (DIT) in place of IT MTX, or TIT in place of double IT.

In the light of the results of the comparison of TIT versus IT MTX therapy, this group of trials was split post-hoc into three subgroups: (a) CRT + IT versus extra IT, (b) CRT + IT MTX versus DIT or TIT, and (c) CRT + DIT versus TIT. We found heterogeneity among subgroups for CNS relapse (p=0.01).

C. *Addition of IV methotrexate (doses ≥ 500 mg/m2) to long-term IT therapy or radiotherapy with IT therapy*. Ten trials with 4140 patients addressed this question, including two new trials. One trial (CCG-163d) previously included was discovered to be confounded, with other chemotherapy differences between the arms with and without IV MTX, and so it has now been excluded in the analysis. One trial (POG9005), which was previously in the 'other comparisons without data' category, is now included because most protocols specified some additional low dose oral MTX in the control arm and this is considered not an important confounding factor.

Again, in the light of the IT MTX versus TIT results, this comparison of the addition of IV methotrexate was split into three groups according to the background treatment: (a) TIT therapy, sometimes plus IV mercaptopurine (MP) and/or some IV methotrexate, (b) IT MTX, and (c) CRT plus IT MTX or TIT therapy. Heterogeneity of effect between subgroups was seen for EFS (p=0.01). Excluding group c, heterogeneity was seen between groups a and b for both CNS (p=0.06) and non-CNS relapse (p=0.008).

D. *IV methotrexate plus IT MTX therapy versus triple IT therapy*. Data were newly available for one trial, previously included in the 'other comparison' group, involving 1159 patients.

E. *Addition of IT therapy to treatment including radiotherapy and short term IT therapy*. Data were available for 1174 patients in two trials out of the four addressing this, previously included in the 'other comparisons group'.

F. *Radiotherapy plus IT therapy versus IV methotrexate plus IT therapy*. Trials comparing CRT with IV MTX were grouped together on the assumption that small differences in IT therapy do not have a major impact. Data for eight trials (including one new trial), involving 1635 patients, were available.

G. *Higher dose of IV methotrexate*. Two new trials, both including TIT therapy for all patients and totally involving 1071 patients, addressed this treatment.

H. *Higher doses of radiotherapy*. Data were available for all eight trials, including one previously without data (GBTLI-80), involving 905 patients. Comparisons were of 24 Gy versus 21 or 18 Gy, except for one trial comparing 18 Gy versus 12 Gy.

I. *Addition of radiotherapy*. Data, involving 664 patients, were available for three of the eight trials addressing this question, including one new trial (CCG-123). These were previously included in the 'other comparison' group. Significant heterogeneity was found for the effect on CNS relapse between (a) CCG trials, which used only IT therapy, and (b) the EORTC 58832 trial, which included IV MTX in both arms (p=0.0003). Therefore this comparison was split.

J. *Higher dose of IV methotrexate versus more IT therapy*. Two trials, involving 700 patients, previously included in 'other comparisons' are grouped here. One used double IT and the other IT MTX.

K. *Addition of IV methotrexate plus IT therapy to radiotherapy plus IT therapy and/or IV methotrexate*. Three trials involving 511 patients addressed this.

Outcomes

Except as stated, treatment effects were similar in different gender, age, WBC, and immunophenotype subgroups. Figures 1A (groups A, Ba, Bb, Ca, Cb), 1B (groups Cc, D, E, F, G), and 1C (groups H, Ia, Ib, J, K) show the treatment effects on EFS for each trial, and for each comparison group. Table S4 shows outcome for all event types according to treatment and results are summarized in Table II. Only 12 trials reported secondary tumour data, which, if included, would have added 21 events.

Radiotherapy

Early trials, mostly of 24 Gy versus 18 or 21 Gy, indicated no evidence that higher dose CRT offers any advantage (comparison H). No significant differences were found for any endpoints (Tables II, S4, Figure 1C).

Where only short-term IT was used (i.e. 6 or 7 doses) (Comparison Ia), CRT significantly reduced the CNS relapse rate (OR=0.28; 95% CI=0.18-0.43; p<0.00001) (Tables II, S4). The non-CNS relapse rates were similar and hence the overall event rate was reduced (p=0.003), resulting in a long term EFS benefit (Figure 1C). There was evidence of possible heterogeneity (p=0.02) between those aged <10 and ≥ 10 years, with the larger effect in younger patients where a larger proportion of the relapses involved the CNS. Survival from relapse was poorer for those relapsing after CRT so that OS was not significantly improved. Replacing CRT with additional IT doses (Comparison Ba) showed that CRT reduced CNS relapse (OR=0.68; 95% CI=0.51-0.92; p=0.01) with no difference in non-CNS relapse

(Tables II, S4). As CNS relapse was a relatively rare event in these trials, no significant EFS difference emerges (Figure 1A). Survival from CNS relapse was non-significantly worse following CRT (p=0.08), while there was no difference in survival from non-CNS relapse, resulting in no difference in OS (Table S4).

Alternatively, in trials replacing CRT with IV MTX (Comparison F), CRT reduced CNS relapse (OR=0.43; 95% CI 0.34-0.56; p<0.0001) but was less effective than IV MTX for non-CNS relapse (OR=1.54; 95% CI 1.27-1.86; p=0.00001) (Tables II, S4). This resulted in similar overall EFS rates (OR=0.95; 95% CI=0.81-1.09, Figure 1B). Survival from relapse was non-significantly worse for CNS relapse after CRT compared with after IV methotrexate, but better for non-CNS relapse, and there was no difference in OS.

Comparisons of CRT plus IT with DIT or TIT (Comparison Bb) or CRT plus DIT with TIT (Comparison Bc) included only small numbers (n=225, 156, respectively). In the first group, CRT appeared to result in poorer OS (OR=1.53; 95% CI=1.01-2.30; p=0.04) (Tables II, S4) but no significant differences were found for any other endpoint. In the second group, CRT plus DIT yielded better CNS control (OR=0.13; 95% CI=0.02-0.93) but there was no difference in EFS or OS (Tables II, S4) and this is based on only one trial including 156 patients and four CNS relapses. When IV MTX was given, no benefit was seen with CRT (Comparison Ib), but fewer than 200 patients were randomized (Tables II, S4).

Combining additional CNS therapy with CRT

If CRT was included in treatment, along with some IT therapy, EFS rates were not improved with addition of further IT doses (OR=0.93; 95% CI=0.77-1.12) (Comparison E, Tables II, S4, Figure 1B). No significant differences were found for any endpoints (Table S4).

No significant differences were found for any endpoints in the comparison of CRT plus IT therapy and/or IV MTX with IV MTX plus IT therapy, although numbers are limited (Comparison K, Tables I, S4).

Two trials looked at the addition of IV MTX to therapy including CRT, one trial with craniospinal irradiation plus IT MTX therapy and the other with cranial irradiation plus TIT (Comparison Cc). Although only 375 patients were randomized there was a reduction in CNS relapse (OR=0.39; 95% CI=0.20-0.79), EFS benefit (OR=0.64; 95% CI=0.43-0.95; p=0.03), and possibly improved OS (p=0.09) (Tables II, S4, Figure 1B). The majority of patients in this comparison were T lineage ALL.

Treatment without CRT

The one large trial of TIT versus IT MTX (Comparison A) showed that CNS relapses were reduced by one third with TIT (OR=0.66; 95% CI 0.47-0.93; p=0.02), but non-CNS relapses were increased by three quarters (OR=1.73; 95% CI 1.30-2.29; p=0.0002) (Tables II, S4), and there was no difference in EFS (p=0.3) (Figure 1A). TIT resulted in worse OS (OR=1.50; 95% CI 1.09-2.06; p=0.01; 2.8% absolute difference) (Figure 2), due partly to worse post-relapse survival for non-CNS as opposed to CNS relapse with either treatment, but also to poorer survival for each relapse type after relapse on TIT (OR=1.84; 95% CI 1.01-3.35; p=0.05 after CNS, OR=1.30; 95% CI 0.83-2.05; p=0.3 after non-CNS relapse).

Adding IV MTX to TIT (Comparison Ca) reduced the overall event rate by a third (OR=0.65; 95% CI=0.53-0.80; p=0.00005) (Figure 1A) due to a reduction in both CNS and non-CNS relapses (Tables II, S4), and resulting in absolute difference of 8.2% in EFS and 3.6% in OS (Figure 3). Where all patients received IT MTX therapy (Comparison Cb), there was no apparent benefit for IV MTX (EFS: OR=0.93; 95% CI=0.80-1.08; p=0.3; Figures 1A, 4), although the rate of CNS relapses may be somewhat lower (OR=0.78; 95%

CI=0.60-1.01; p=0.06) (Tables II, S4). No differences were found for survival from relapse or OS in either of these comparisons.

In one large trial comparing IV MTX plus IT therapy with TIT alone (Comparison D), CNS relapse was higher with IV MTX plus IT MTX (OR=1.64; 95% CI 1.13-2.39; p=0.01) (Tables II, S4) but the lower non-CNS relapse rate, albeit not significant, resulted in similar EFS (OR=0.98; 95% CI=0.82-1.17, Figure 1B) and OS.

In the comparison of higher dose IV MTX (i.e. 2.5 g/m^2 versus 1 g/m^2) (Comparison G), no significant differences were found for any endpoint, including EFS (OR=0.93; 95% CI=0.74-1.16) (Tables II, S4, Figure 1B).

Similarly, comparisons of high dose IV MTX (8g/m^2) with lower dose (3g/m^2) plus IT MTX or DIT (Comparison J) showed no significant differences for any endpoint (Tables II, S4).

DISCUSSION

This study demonstrated that effective systemic and IT chemotherapy can yield EFS at least comparable to that of CRT with or without additional IT therapy; the findings extend those of the previous meta-analysis showing that CRT could generally be replaced by long term IT therapy, with some additional benefit from the addition of IV MTX[5]. Historically, the introduction of CRT was a major breakthrough, but there is no evidence that higher dose CRT offers any advantage. Although the addition of CRT to short term IT (≤8 doses) treatment showed benefit in early trials, alternative therapy, such as giving additional IT doses or IV MTX can be as effective in terms of EFS and OS. In CCG-105, the omission of CRT diminished EFS for those receiving standard (minimal) therapy but not for those receiving more intensive BFM-based treatment[13]. Therefore the ability to omit CRT depends on systemic as well as IT therapy. Even if CRT is used, there was some evidence, mainly in T-lineage disease, that the addition of IV MTX to CRT might improve EFS further for some patients.

There was no direct evidence on the comparative effectiveness of IT MTX, DIT and TIT in the previous meta-analysis. The CCG-1952 trial has now provided some evidence on TIT versus IT MTX which has suggested that other comparison groups should be split, and this has been confirmed by heterogeneity tests between the revised subgroups. On the other hand, different IT therapies are grouped together in the comparisons between trials with CRT and those with IV MTX on the assumption that small differences in IT MTX, DIT, TIT therapies will have minor effects compared with those of CRT and IV MTX. Direct evidence comparing doses of IV MTX has also become available.

When neither CRT nor IV MTX are used, CCG 1952 study showed that, compared with IT MTX, TIT reduced the frequency of isolated CNS relapse. The impact of TIT on isolated CNS relapse was especially pronounced in patients with CNS2 status such that it reduced 6-year cumulative risk to 7.7%±5.3% as compared to 23.0%±9.5% among those treated with IT MTX (P=0.004); the 6-year cumulative risk of isolated CNS relapse among patients with CNS1 status was 3.1%±1.0% versus 5.1%±1.2% between those treated with TIT or IT MTX (P=0.03)[10]. However, TIT treatment was unexpectedly associated with an increased frequency of bone marrow and testicular relapse, resulting in similar EFS and poorer OS. One explanation for this seemingly paradoxical finding is that cytarabine or hydrocortisone in TIT interferes with egress of MTX from cerebrospinal fluid into blood such that patients receiving TIT had less systemic exposure to MTX[10]. Another explanation is that CNS relapse and other relapses are competing events so that improved CNS control by TIT might have led to leukemic relapse in other sites. In this regard, adding IV MTX to TIT improved

outcome by reducing both CNS and non-CNS relapses, whereas adding IV to IT had little effect. Only one trial compared IV MTX plus IT with TIT, with no EFS or OS difference. It may be that more effective systemic therapy is needed before the full benefit of TIT can be realized. COG is re-examining the question of TIT in the B-precursor higher risk trial, AALL1131. All patients will receive IV MTX at 5 g/m^2 with leucovorin and the more favourable patients by presenting features and response will be randomized to receive IT MTX versus TIT.

That higher dose of IV MTX failed to significantly improve EFS in some studies might be due to excessive leucovorin rescue[24,57,58]. In this regard, it is of special interest that even lower dose IV MTX, without leucovorin, on CCG-1991 (100-300 mg/m^2) can reduce CNS relapse[59]. This trial was in NCI standard risk patients and compared two courses of interim maintenance with five doses of vincristine plus IV MTX at 100 mg/m^2 escalated by 50 mg/m^2 every ten days for four doses as tolerated, versus oral mercaptopurine, oral methotrexate plus ten doses of dexamethasone at six mg/m^2 and reported an EFS advantage with escalating IV MTX. However, the recent COG AALL0232 trial in NCI high risk patients up to the age of 30 years shows a substantial EFS advantage for IV MTX at 5 g/m^2 with leucovorin rescue compared with asparaginase plus escalating IV MTX without rescue[60,61]. This trial also randomized between dexamethasone and prednisone. The final report is not yet available, but there appears to be an interaction suggesting EFS benefit only for the high dose IV MTX plus dexamethasone combination. In this regard, when high dose IV MTX is used, attention needs to be paid to the leucovorin rescue, keeping it to the minimum necessary.

Despite impressive gains from the treatment of childhood ALL, there is still a need to improve management of CNS disease so that cranial irradiation can be avoided in all children. In this regard, both intrathecal and systemic therapy must be optimized in order to achieve the goal. Dexamethasone, high dose cytarabine and asparaginase may all be relevant. With improved systemic therapy, future studies should determine the optimal number of intrathecal therapy because this treatment modality can also adversely affect neurocognitive function. However, a certain number of intrathecal therapy doses are necessary because high dose methotrexate alone, even at very high dose (33.6 g/m2), was inadequate for CNS control[62]. To answer outstanding questions it would be helpful for future trials to be designed so that randomized comparisons address single drugs as far as possible.

No clear subgroup differences exist, but information is limited, particularly for T-lineage ALL. An effective CNS-directed treatment strategy without concomitant adequate systemic therapy may lead to increased bone marrow relapse and poorer OS. Thus, the combination of CNS and systemic effects, as well as outcome post relapse, need to always be borne in mind.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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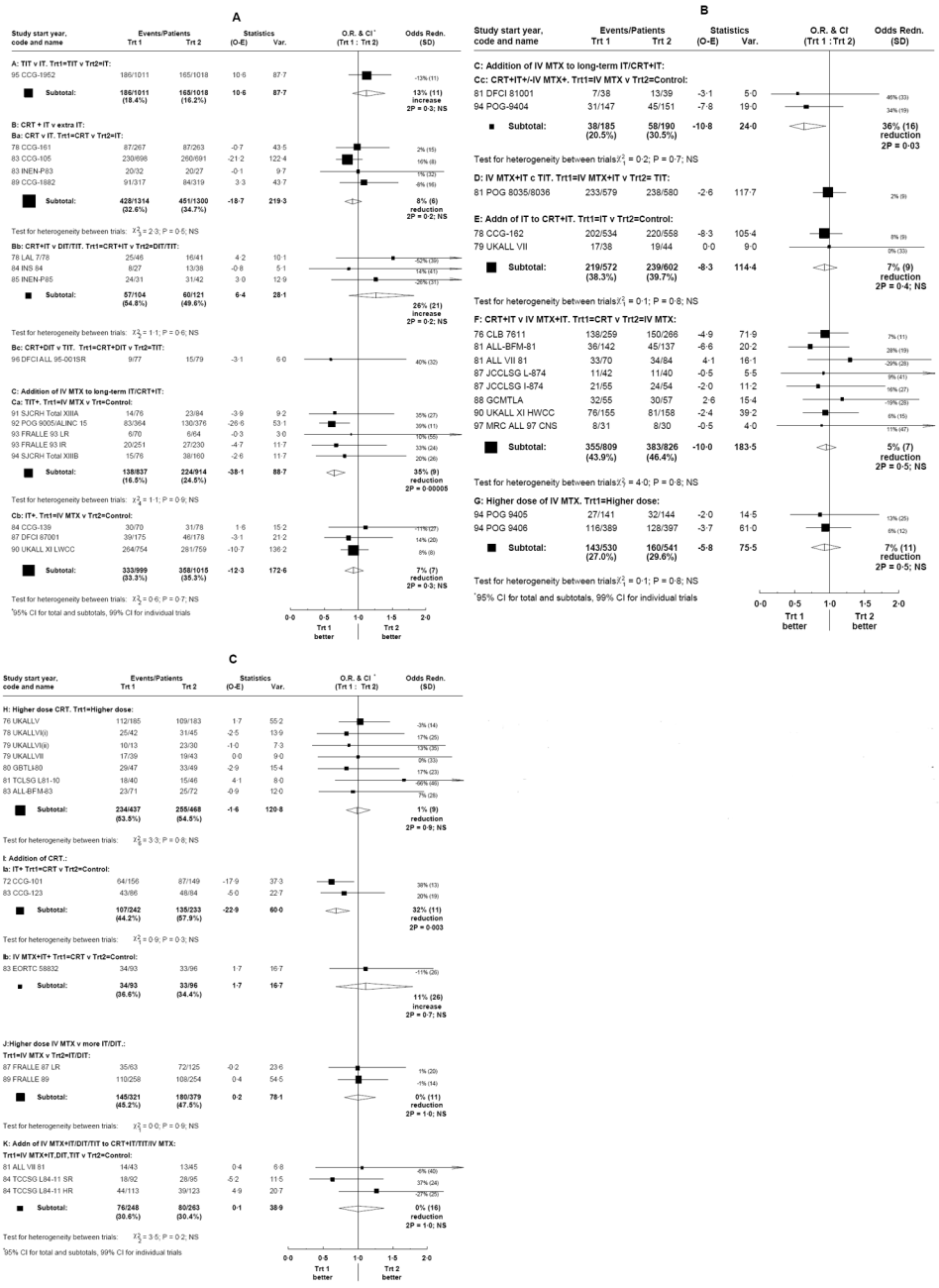
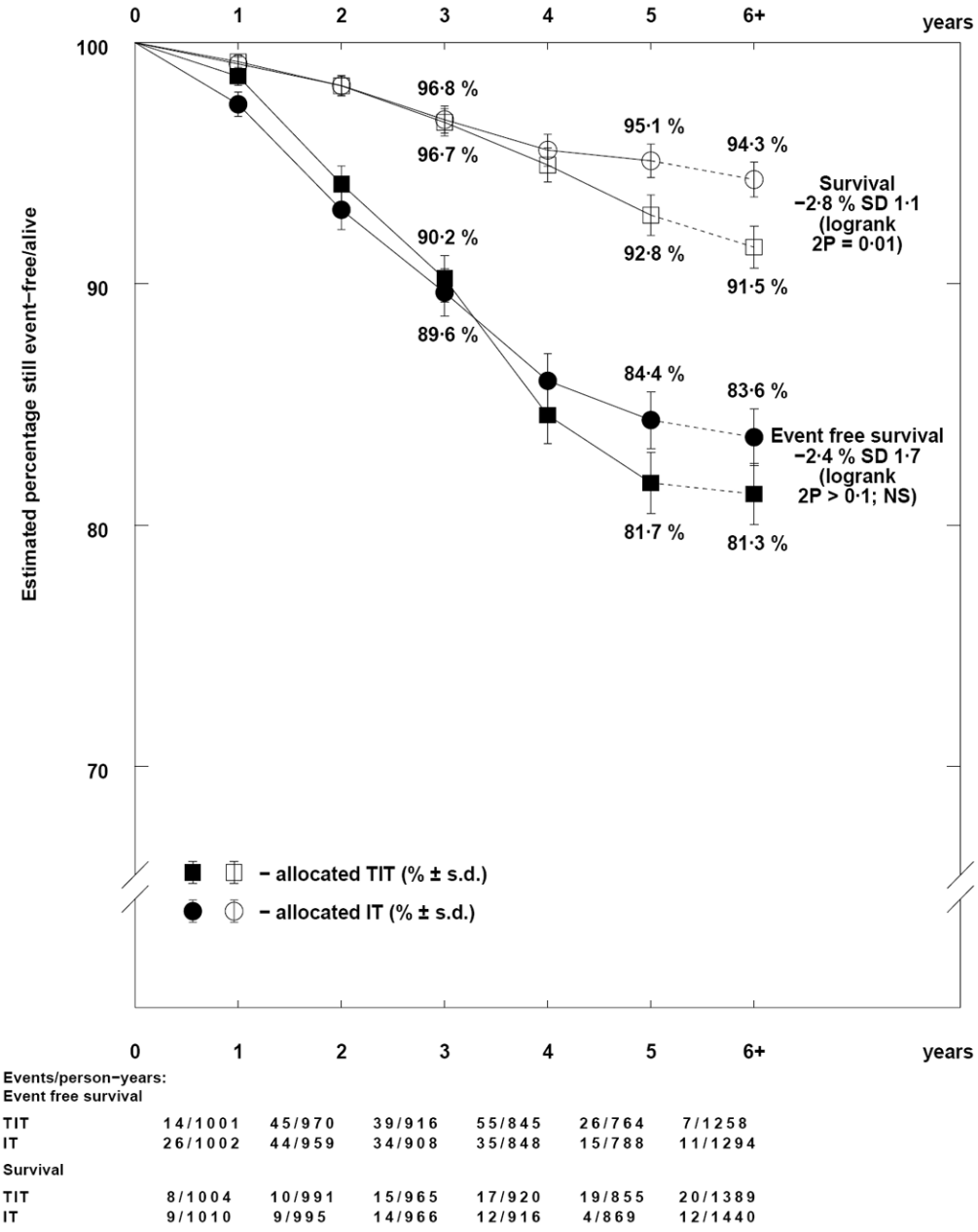


Figure 1.

Effects of treatments on event free survival. Ratios of annual event rates with each trial result represented by a square, with larger squares indicating more information, and the overall result for each comparison represented by a diamond.



Events/person−years: Event free survival						
TIT	14/1001	45/970	39/916	55/845	26/764	7/1258
IT	26/1002	44/959	34/908	35/848	15/788	11/1294
Survival						
TIT	8/1004	10/991	15/965	17/920	19/855	20/1389
IT	9/1010	9/995	14/966	12/916	4/869	12/1440

Figure 2.
Descriptive event free and overall survival curves for TIT versus IT therapy.

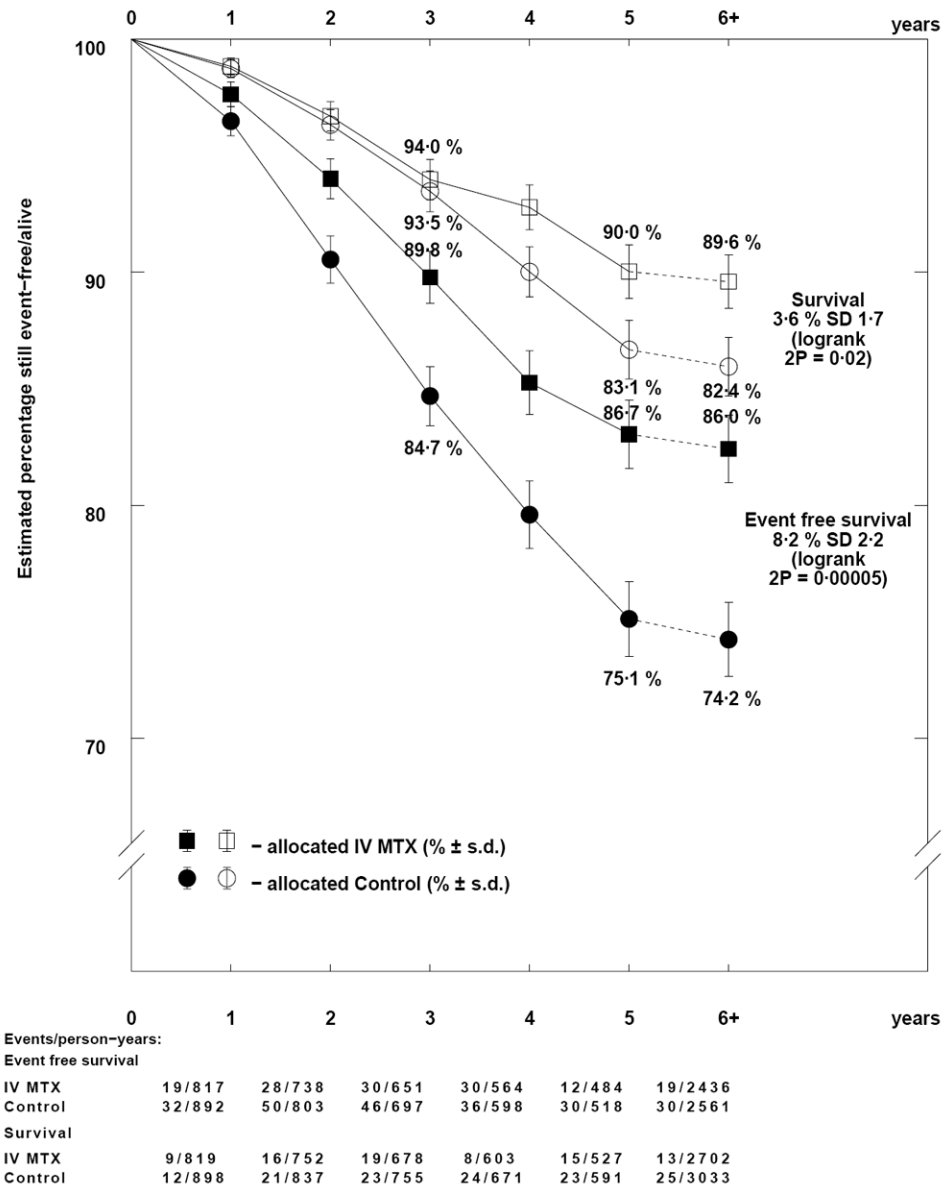


Figure 3.
Descriptive event free and overall survival curves for the addition of IV methotrexate to TIT.

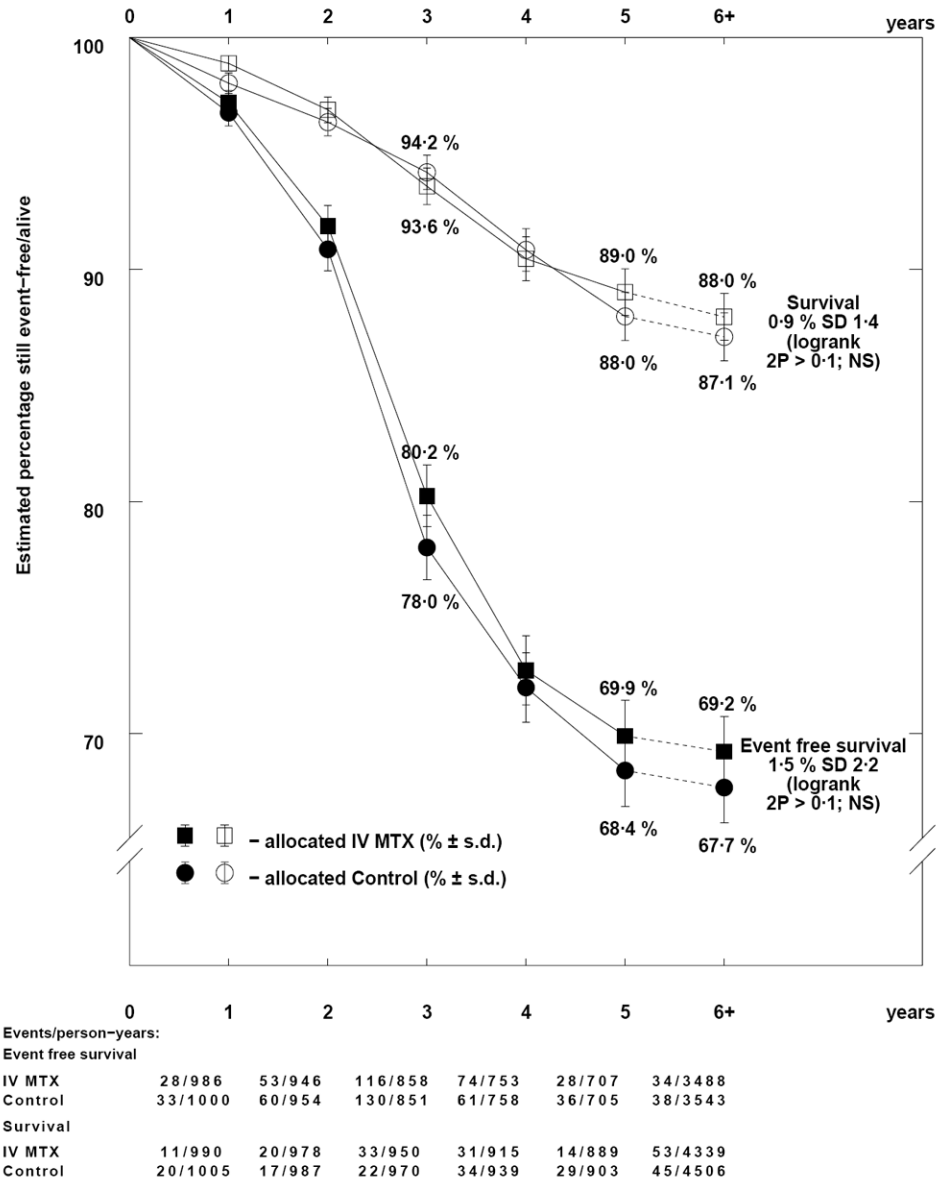


Figure 4.
Descriptive event free and overall survival curves for the addition of IV methotrexate to IT therapy.

Table I

Summary of CNS-directed treatments

Trial	Year	Ref	CNS-directed therapy
A: TIT versus IT therapy			
*CCG-1952	1996	11	DITa × 1 + IT MTX × 1 R: TITa × 14 (f) or 18 (m) v IT MTX × 14 (f) or 18 (m)
B: Radiotherapy plus IT therapy versus extra IT therapy			
a Radiotherapy v IT therapy			
CCG-161	1978	12	IT MTX × 6 R: 18 Gy CRT v IT MTX × 8
CCG-105	1983	13	IT MTX × 6 R: 18 Gy CRT v IT MTX × 8 (f) or 14 (m)
INEN-P83	1983		IT MTX × 5 R: 18 Gy CRT v IT MTX × 12
CCG-1882	1989	14	IT MTX × 14 (f) or 18 (m) + IT AraC × 1 R: 18 Gy CRT v IT MTX × 7
b Radiotherapy (+ IT) v DIT or TIT therapy			
†SWOG 7623/AlinC12	1976	15	R: 24 Gy CRT + IT MTX × 5 v TITa × 22
LAL 7/78	1978	16	R: 24 Gy CRT + IT MTX × 6 v DITa × 10
INS 84	1984	17	TITa × 6 R: 18Gy CRT v TITa × 12
INEN-P85	1985		R: 18 Gy CRT + IT MTX × 5 v TITa × 17
c Radiotherapy + DIT v TIT therapy			
*DFCI ALL 95-001	1996	18	IT AraC × 1 + TITa × 2 R: 18Gy CRT + DITa × 6 v TITa × 12
C: Addition of IV methotrexate to long-term IT therapy or radiotherapy with IT therapy			
a TIT therapy +/- IV methotrexate			
SJCRH Total XIIIA	1991	19	TITa × 13 or 17 + 2 g/m^{2}IV MTX × 9 or 10 R: ± 1 g/m^2 IV MTX × 1
*POG 9005	1991	20	1 g/m^2 IV mp × 17–19 + TITA × 16 R: ± 1 g/m^2 IV MTX × 12
FRALLE 93 LR	1993	21	TITc × 16 R: ± 1·5 g/m^2 IV MTX × 6
FRALLE 93 IR	1993	21	TITc × 18 R: ± 8 g/m^2 IV MTX × 4
*SJCRH Total XIIIB	1994	22	1 g/m^2 IV mp + TITa × 13 or 15 + 2 g/m^2 IV MTX × 10 R: ± 1 g/m^2 IV MTX × 1
b IT therapy +/- IV methotrexate			
CCG-139	1984	23	IT MTX × 15 (f) or 20 (m) R: ± 0·5 g/m^2 IV MTX × 24 (f) or 33 (m)
DFCI 87001	1987	24	IT AraC × 1 + IT MTX × 10 (HR: + 18 Gy CRT) R: ± 4 g/m^2 IV MTX × 1
UKALLXI LWCC	1990	25	IT MTX × 16 R: ± 6–8 g/m^2 IV MTX × 3
c Radiotherapy with IT therapy +/- IV methotrexate			

Trial	Year	Ref	CNS-directed therapy
DFCI 81001	1981	26	18 or 28 Gy CSCRT + IT AraC × 1 + IT MTX × 8 R: ± 4 g/m^{2}IV MTX × 1
*POG 9404	1994	27	TITa × 11 + 18 Gy CRT R: ± 5 g/m^2 IV MTX × 4
D: IV methotrexate + IT therapy v TIT			
*POG8035/8036	1981	28	TITa × 6 R: 1 g/m^2 IV MTX × 17 + IT MTX × 4 v TITa × 17
E: Addition of IT therapy to radiotherapy plus short-term IT therapy			
†CALGB-7113	1971	29	24 Gy CRT + IT MTX × 12 R: ± IT MTX × 3
CCG-162	1978	30	18 Gy CRT + IT MTX × 6 R: ± IT MTX × 8
UKALLVII	1979	31	18 or 24 Gy CRT + IT MTX × 5 R: ± IT MTX × 8
F: Radiotherapy plus IT therapy v IV methotrexate plus IT therapy			
CLB 7611	1976	32	IT MTX × 6 R: 24 Gy CRT v 0·5 g/m^2 IV MTX × 3
†NCI 77-02	1980	33	R: 18–24 Gy CRT + IT MTX × 5 v 33·6 g/m^2 IV MTX × 10
ALL-BFM-81	1981	34	IT MTX × 6 R: 12–18 Gy CRT v 0·5 g/m^2 IV MTX × 4
Jena ALL VII 81	1981	35	IT MTX × 8 R: 18 Gy CRT v 0·5 g/m^2 IV MTX × 4
JCCLSG L-874	1987	36	DITb × 3 R: 18 Gy CRT v 2 g/m^2 IV MTX × 3 + DITb × 6
JCCLSG I-874	1987	36	(2 g/m^2 × 1 + 4·5 g/m^2 × 20) IV MTX + DITb × 1 R: 18 Gy CRT + DITb × 2 v 4·5 g/m^2 IV MTX × 3
GCMTLA	1988	37	TITb × 6 R: 12–18 Gy CRT v 0·5 g/m^2 IV MTX × 4 + TITb × 6
†TCCSG L89-12	1989	38	TITa × 4 + DITa × 3 R: 18 Gy CRT v 3 g/m^2 IV MTX
UKALLXI HWCC	1990	25	IT MTX × 7 or 9 R: 24 Gy CRT v 6–8 g/m^2 IV MTX × 3 + IT MTX × 8 or 9
†TCCSG L92-13 HR	1992	38	DITb × 4 + TITa × 3 R: 18 Gy CRT + DITb × 1 v 3 g/m^2 IV MTX × 2
*MRC ALL97	1997	39	IT MTX × 7 or 9 R: 24 Gy CRT v 6–8 g/m^2 IV MTX × 3 + IT MTX × 8 or 9
G: Higher dose of IV methotrexate			
*POG 9405	1994	40	TITa × 22 R: 2·5 g/m^2 IV MTX × 12 v 1 g/m^2 IV MTX × 12
*POG 9406	1994	40	TITa × 18 + 1 g/m^2 IV mp × 6 R: 2·5 g/m^2 IV MTX × 6 v 1 g/m^2 IV MTX × 6
H: Higher doses of radiotherapy			
UKALL V	1976	41	IT MTX × 5 R: 24 Gy v 21 Gy CRT
UKALLVI(i)	1978	42	IT MTX × 8 or IT MTX × 6 + IT AraC × 2 + 0·5 g/m^2 IV MTX × 3 R: 24 Gy v 21 Gy CRT
UKALLVI(ii)	1978	42	IT MTX × 8 or IT MTX × 6 + IT AraC × 2 + 0·5 g/m^2 IV MTX × 3 R: 24 Gy v 18 Gy CRT
UKALLVII	1979	31	IT MTX × 5 R: 24 Gy v 18 Gy CRT
GBTLI-80	1980	43	IT MTX × 13 R: 24 Gy v 18 Gy CRT

Trial	Year	Ref	CNS-directed therapy
TCCSG L81-10	1981	44	DITa × 5 R: 24 Gy v 18 Gy CRT
ALL-BFM-83	1983	34	IT MTX × 8 + 0·5 g/m^2 IV MTX × 4 R: 18 Gy v 12 Gy CRT
I: Addition of radiotherapy			
a Addition to IT			
†POG CNS2	1970	45	IT MTX × 20 R: ± 24 Gy CRT
†CLB 7111	1971	46	IT MTX × 6 R: ± 24 Gy CRT
†SWOG 690/691/Alinc9	1971	47	TITa × 10 R: ± 18–24 Gy CRT
†DFCI-SFCC	1972	48	IT MTX × 9 R: ± 24 Gy CRT
†CLB 7411	1974	49	IT MTX × 6 R: ± 24 Gy CRT
CCG-101	1974	50	IT MTX × 6 R: ± 24 Gy CRT
*CCG-123	1983	51	IT AraC × 1 + IT MTX × 6 R: ± 18Gy CRT
b Addition to IV with IT			
EORTC 58832	1983	52	2·5 g/m^2 IV MTX × 4 + IT MTX × 7 R: ± 16–20 Gy CRT
J: Higher dose of IV methotrexate v more IT or DIT therapy			
FRALLE 87	1987	53	DITc × 5 R: 8 g/m^2 IV MTX × 4 v 3 g/m^2 IV MTX × 4 + DITc × 5
FRALLE 89	1989	21	IT MTX × 5 R: 8 g/m^{2}IV MTX × 4 v 3 g/m^{2}IV MTX × 4 + IT MTX × 5
K: Addition of IV methotrexate plus IT, DIT or TIT therapy to radiotherapy plus IT or TIT therapy and/or IV methotrexate			
Jena ALLVII 81	1981	35	12 or 18 Gy CRT + IT MTX × 8 R: ± 0·5 g/m^2 IV MTX × 4 + IT MTX × 4
TCCSG L84-11 SR	1984	38	18 Gy CRT + TITa × 5 + 0·5 g/m^2 IV MTX × 4 + IT MTX × 4 R: ± 0·5 g/m^2 IV MTX × 3 + DITb × 6
TCCSG L84-11 HR	1984	38	24 Gy CRT + TITa × 5 + 0·5g/m^2 IV MTX × 12 + DITb × 12 R: ± 0·5 g/m^2 IV MTX × 3 + TITa × 6
Other comparisons without data			
†ALGB 6801	1968	54	R: IT MTX × 15
†GATLA-70	1970	55	R: ± 24 Gy CRT + IT MTX × 5
†NCI 72-1	1971	56	24 Gy CRT R: IT AraC × 38 v IT MTX × 35
†NCI-84-C-153A	1984		R: 33·6 g/m^2 IV MTX × 10 v IT MTX × 8

†Data not available;

*Not in previous paper; AraC, cytosine arabinoside; CRT, cranial irradiation; CSCRT, craniospinal irradiation; DITa, IT MTX + IT AraC; DITb, IT MTX + IT Hc; DITc, IT MTX + IT P; Dx, dexamethasone; f, female; Hc, hydrocortisone; IT, intrathecal; m, male; mp, mercaptopurine; MTX, methotrexate; P, prednisone; R, randomization; TITa, IT MTX + IT AraC + IT Hc; TITb, IT MTX + IT AraC + IT Dx; TITc, IT MTX + IT AraC + IT P.

Table II

Summary results

Trial	Background CNS treatment	Arm 1	Arm 2*	Conclusions
A: TIT versus IT therapy (n=2029)				
CCG-1952[11]	DIT × 1 + IT × 1	TIT × 14 (f) or 18 (m)	IT × 14 (f) or 18 (m)	TIT reduced CNS relapse compared with IT but an increase in non-CNS relapse resulted in similar EFS and worse OS (OR=1·50; p=0·01).
Ba: Radiotherapy plus short-term IT therapy versus extra IT therapy (n=2614)				
CCG-161[12]	IT × 6	CRT	IT × 8	Adding CRT to short-term IT reduced CNS relapses (OR=0·68; p=0·01) compared with adding more IT doses, but did not substantially affect EFS (OR=0·92; 95% CI = 0·80 1·05; p=0·2).
CCG-105[13]	IT × 6	CRT	IT × 8 (f) or 14 (m)	
INEN-P83	IT × 5	CRT	IT × 12	
CCG-1882[14]	IT × 15 (f) or 19 (m)	CRT	IT × 7	
Bb: Radiotherapy plus short-term IT therapy versus DIT or TIT (n=234)				
LAL 7/78[16]		CRT + IT × 6	DIT × 10	Small numbers make results uncertain but OS was worse with CRT (OR=1·63; p=0·02)
INS 84[17]	TIT × 6	CRT	TIT × 12	
INEN-P85		CRT + IT × 5	TIT × 17	
Bc: Radiotherapy plus DIT versus extra TIT (n=155)				
DFCI ALL 95-001[18]	IT × 1 + TIT × 2	CRT + DIT × 6	TIT × 12	Insufficient data to draw any conclusions.
Ca: Addition of IV methotrexate to TIT or TIT with IV methotrexate (n=1751)				
SJCRH Total XIIIA[19]	TIT × 13 or 17 + IV × 9 or 10	IV × 1	Control	Adding IV MTX to TIT reduced both CNS (OR=0·48; p=0·0009) and non-CNS relapse (OR=0·65; p=0·002), giving better EFS (OR=0·65; p=0·00005) and OS (OR=0·71; p=0·02)
POG 9005[20]	IV mp × 17–19 + TIT × 16	IV × 12	Control	
FRALLE 93 LR[21]	TIT × 16	IV × 6	Control	
FRALLE 93 IR[21]	TIT × 18	IV × 4	Control	
SJCRH Total XIIIB[22]	IV mp + TIT × 13 or 15 + IV × 10	IV × 1	Control	
Cb: Addition of IV methotrexate to long-term IT therapy (n=2014)				
CCG-139[23]	IT × 15 (f) or 20 (m)	IV × 24 (f) or 33 (m)	Control	Adding IV MTX to long-term IT probably reduced CNS relapse (OR=0·78; p=0·06), but did not improve EFS or OS.
DFCI 87001[24]	IT × 11 (HR: + CRT)	IV × 1	Control	
UKALLXI LWCC[25]	IT × 16	IV × 3	Control	
Cc: Addition of IV methotrexate to radiotherapy with TIT or IT therapy (n=375)				

Trial	Background CNS treatment	Arm 1	Arm 2*	Conclusions
DFCI 81001[26]	CSCRT + IT × 9	IV × 1	Control	Adding IV MTX to CRT with short-term IT or TIT reduced CNS relapses (OR=0·39; p=0·008) and improved EFS (OR=0·64; p=0·03), but small numbers make these results less reliable.
POG 9404[27]	TIT × 11 + CRT	IV × 4	Control	
D: IV methotrexate + IT therapy + TIT versus extra TIT (n=1159)				
POG8035/8036[28]	TIT × 6	IV × 17 + IT × 4	TIT × 17	IV MTX was less effective than extra TIT in preventing CNS relapse (OR=1·64; p=0·01) but the reduction in non-CNS relapse (OR=0·82; p=0·08) resulted in equivalent EFS and OS.
E: Addition of IT therapy to radiotherapy plus short-term IT therapy (n=1174)				
CCG-162[30]	CRT + IT × 6	IT × 8	Control	Adding extra IT therapy to CRT with short-term IT did not give benefit.
UKALLVII[31]	CRT + IT × 5	IT × 8	Control	
F: Radiotherapy versus IV methotrexate: short-term IT, DIT in both arms (IV MTX in one trial) and some additional IT or TIT in the IV MTX arm (n=1635)				
CLB 7611[32]	IT × 6	CRT	IV × 3	CRT given with short-term IT, DIT or TIT, reduced CNS relapse (OR=0·43; p<0·00001) compared with giving IV MTX, with or without extra IT, but non-CNS relapses were increased (OR=1·54; p=0·00001), resulting in no difference in EFS or OS.
ALL-BFM-81[34]	IT × 6	CRT	IV × 4	
Jena ALL VII 81[35]	IT × 8	CRT	IV × 4	
JCCLSG L-874[36]	DIT × 3	CRT	IV × 3 + TIT × 6	
JCCLSG I-874[36]	IV × 21+ DIT × 1	CRT + DIT × 2	IV × 3	
GCMTLA[37]	TIT ×6	CRT	IV × 4 + TIT × 6	
UKALLXI HWCC[25]	IT × 7 or 9	CRT	IV × 3 + IT × 8 or 9	
MRC ALL97[39]	IT × 7 or 9	CRT	IV × 3 + IT × 8 or 9	
G: Higher dose of IV methotrexate (n=1071)				
POG 9405[40]	TIT × 22	2·5 g/m^2 IV × 12	1 g/m^2 IV × 12	No benefit from higher dose of IV MTX.
POG 9406[40]	TIT × 18 + 1 g/m^2 IV mp × 6	2·5 g/m^2 IV × 6	1 g/m^2 IV × 6	
H: Higher doses of radiotherapy (n=905)				
UKALL V[41]	IT × 5	24 Gy CRT	21 Gy CRT	No benefit from higher doses of CRT.
UKALLVI(i)[42]	IT × 10 or IT × 8 + IV × 3	24 Gy CRT	21 Gy CRT	
UKALLVI(ii)[42]	IT × 10 or IT × 8 + IV × 3	24 Gy CRT	18 Gy CRT	
UKALLVII[31]	IT × 5	24 Gy CRT	18 Gy CRT	
GBTLI-80[43]	IT × 13	24 Gy CRT	18 Gy CRT	
TCCSG L81-10[44]	DIT × 5	24 Gy CRT	18 Gy CRT	

Trial	Background CNS treatment	Arm 1	Arm 2*	Conclusions
ALL-BFM-83[34]	IT × 8 + IV × 4	18 Gy CRT	12 Gy CRT	
Ia: Addition of radiotherapy to short-term IT therapy (n=475)				
CCG-101[50]	IT × 6	CRT	Control	Adding CRT to 6 or 7 doses of IT reduced CNS relapses (OR=0·28; p <0·00001) and improved EFS (OR=0·68; p=0·003)
CCG-123[51]	IT × 7	CRT	Control	
Ib: Addition of radiotherapy to IV methotrexate plus IT therapy (n=189)				
EORTC 58832[52]	IV × 4 + IT × 7	CRT	Control	Insufficient data to draw any conclusions.
J: Higher dose of IV methotrexate versus more IT or DIT therapy (n=700)				
FRALLE 87[53]	DIT × 5	8 g/m^2 IV × 4	3 g/m^2 IV × 4 + DIT × 5	There was no evidence of a difference between high dose and a lower dose with extra IT or DIT.
FRALLE 89[21]	IT × 5	8 g/m^{2}IV × 4	3 g/m^{2}IV × 4 + IT × 5	
K: Addition of IV methotrexate plus IT, DIT or TIT therapy to radiotherapy plus IT or TIT therapy and/or IV methotrexate (n=511)				
Jena ALLVII 81[35]	CRT + IT × 8	IV × 4 + IT × 4	Control	There was no evidence of a benefit from adding IV MTX with extra IT, DIT or TIT to a treatment which included CRT.
TCCSG L84-11 SR[38]	CRT + TIT × 5 + IV × 4 + IT × 4	IV × 3 + DIT × 6	Control	
TCCSG L84-11 HR[38]	CRT + TIT × 5 + IV × 12 + DIT × 12	IV × 3 + TIT × 6	Control	

*Arm 2 = Control indicates that no CNS treatment was given additional to the background.

CRT, cranial irradiation; CSCRT, craniospinal irradiation; DIT, double intrathecal; f, female; IT, intrathecal; IV, intravenous methotrexate; IV mp, intravenous mercaptopurine; m, male; TIT, triple intrathecal.