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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 increased², 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 necessary¹. In 2003, we performed a collaborative meta-analysis of randomized trials addressing issues of pre-symptomatic CNS therapy that initiated accrual prior to 1994⁵. In this study, we update this work, and include additional trials that commenced before 2000 to allow adequate follow-up time.

CONFLICT OF INTEREST STATEMENT

All members of the writing committee declare there are no conflicts of interest.

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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 steroid⁶⁻⁸ 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 toxicity⁹.

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 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 $\exp(T/V \pm 1.96/V)$. 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-T²/V, where S is the sum of (o-e)²/v from each of n trials or n subgroups¹⁰.

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 group¹⁰.

Trials were categorized *a priori* and the results combined according to the treatment comparisons and background CNS-directed treatments. We examined conventional prespecified 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 treatments¹¹⁻⁵⁶. 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 MTX⁵. 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 treatment¹³. 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 $7.7\% \pm 5.3\%$ as compared to $23.0\% \pm 9.5\%$ among those treated with IT MTX (P=0.004); the 6-year cumulative risk of isolated CNS relapse among patients with CNS1 status was $3.1\% \pm 1.0\%$ versus $5.1\% \pm 1.2\%$ 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 MTX¹⁰. 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/m² 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/m²) can reduce CNS relapse⁵⁹. 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/m² escalated by 50 mg/m² every ten days for four doses as tolerated, versus oral mercaptopurine, oral methotrexate plus ten doses of dexamethasone at six mg/m² 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/m² 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 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 control⁶². 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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References

- 1. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol. 2008; 9:57–68.
- Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. 2008; 111:5515–23. [PubMed: 18334672]
- Veerman AJ, Kamps WA, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). Lancet Oncol. 2009; 10:957–66. [PubMed: 19747876]
- 4. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009; 360:2730–41. [PubMed: 19553647]
- Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lymphoblastic leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. J Clin Oncol. 2003; 21(9):1798–809. [PubMed: 12721257]
- Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood. 2003; 101:3809–17. [PubMed: 12531809]
- Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. British Journal of Haematology. 2005; 129:734–45. [PubMed: 15952999]
- Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. Lancet Oncol. 2010; 11:1096–106. [PubMed: 20947430]
- Escherich G, Richards S, Stork LC, Vora AJ. Meta-analysis of randomised trials comparing thiopurines in childhood acute lymphoblastic leukaemia. Leukemia. 2011; 25(6):953–9. [PubMed: 21372841]
- Early Breast Cancer Trialists' Collaborative Group. Treatment of Early Breast Cancer : Worldwide Evidence 1985-1990. Vol. 1. Oxford, UK: Oxford University Press; 1990. p. 207
- Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. Blood. 2006; 108:1165–73. [PubMed: 16609069]
- Littman P, Coccia P, Bleyer WA, et al. Central nervous system (CNS) prophylaxis in children with low risk acute lymphoblastic leukemia (ALL). Int J Radiat Oncol Biol Phys. 1987; 13:1443–9. [PubMed: 3305443]
- Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk acute lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the importance of systemic therapy: a Childrens Cancer Group report. J Clin Oncol. 1993; 11:520– 6. [PubMed: 8445427]
- Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. J Clin Oncol. 1998; 16:920–30. [PubMed: 9508174]
- van Eys J, Berry D, Crist W, et al. A comparison of two regimens for high-risk acute lymphocytic leukemia in childhood. A Pediatric Oncology Group Study. Cancer. 1989; 63:23–9. [PubMed: 2910421]
- Ortega JJ, Javier G, Olive T. Treatment of standard- and high-risk childhood acute lymphoblastic leukaemia with two CNS prophylaxis regimens. Haematol Blood Transfus. 1987; 30:483–92. [PubMed: 3114061]
- Stark B, Nirel R, Avrahami G, et al. Long-term results of the Israeli National Studies in childhood acute lymphoblastic leukemia: INS 84, 89 and 98. Leukemia. 2010; 24:419–24. [PubMed: 20016534]

- Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood. 2007; 109:896–904. [PubMed: 17003366]
- Masson E, Relling MV, Synold TW, et al. Accumulation of methotrexate polyglutamates in lymphoblasts is a determinant of antileukemic effects in vivo. A rationale for high-dose methotrexate. J Clin Invest. 1996; 97:73–80. [PubMed: 8550853]
- Mahoney DHJ, Shuster JJ, Nitschke R, et al. Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy--a Pediatric Oncology Group study. J Clin Oncol. 1998; 16:1712–22. [PubMed: 9586883]
- Schaison GS, Baruchel A, Leblanc TAM, Leverger G. Therapy of childhood acute lymphoblastic leukemia. Int J Pediatr Hematol Oncol. 1998; 5:145–54.
- Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood. 2004; 104:2690–6. [PubMed: 15251979]
- Lange BJ, Blatt J, Sather HN, Meadows AT. Randomized comparison of moderate-dose methotrexate infusions to oral methotrexate in children with intermediate risk acute lymphoblastic leukemia: a Childrens Cancer Group study. Med Pediatr Oncol. 1996; 27:15–20. [PubMed: 8614385]
- LeClerc JM, Billett AL, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. J Clin Oncol. 2002; 20:237–46. [PubMed: 11773175]
- 25. Hill FG, Richards S, Gibson B, et al. Successful treatment without cranial radiotherapy of children receiving intensified chemotherapy for acute lymphoblastic leukaemia: results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI (ISRC TN 16757172). Br J Haematol. 2004; 124:33–46. [PubMed: 14675406]
- Niemeyer CM, Reiter A, Riehm H, et al. Comparative results of two intensive treatment programs for childhood acute lymphoblastic leukemia: The Berlin-Frankfurt-Munster and Dana-Farber Cancer Institute protocols. Ann Oncol. 1991; 2:745–9. [PubMed: 1801880]
- Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). Blood. 2011; 118:874–83. [PubMed: 21474675]
- Pullen J, Boyett J, Shuster J, et al. Extended triple intrathecal chemotherapy trial for prevention of CNS relapse in good-risk and poor-risk patients with B-progenitor acute lymphoblastic leukemia: a Pediatric Oncology Group study. J of Clin Oncol. 1993; 11:839–49. [PubMed: 8487048]
- Henderson ES, Scharlau C, Cooper MR, et al. Combination chemotherapy and radiotherapy for acute lymphocytic leukemia in adults: results of CALGB protocol 7113. Leuk Res. 1979; 3(6): 395–407. [PubMed: 297176]
- 30. Bleyer WA. Intrathecal methotrexate versus central nervous system leukemia. Cancer Drug Deliv. 1984; 1:157–67. [PubMed: 6399986]
- 31. Medical Research Council leukaemia trial, UKALL VII. A report to the Council by the Working Party on Leukaemia in Childhood. Arch Dis Child. 1985; 60:1050–4. [PubMed: 3907505]
- Freeman AI, Boyett JM, Glicksman AS, et al. Intermediate-dose methotrexate versus cranial irradiation in childhood acute lymphoblastic leukemia: a ten-year follow-up. Med Pediatr Oncol. 1997; 28:98–107. [PubMed: 8986145]
- 33. Poplack DG, Reaman GH, Bleyer WA, et al. CNS preventive therapy with high-dose methotrexate in acute lymphoblastic leukemia: a preliminary report. Proc Am Soc Clin Oncol. 1984; 3(204) abstr 797.
- Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia. 2010; 24:265–84. [PubMed: 20010625]
- 35. Zintl F, Plenert W, Malke H. Results of acute lymphoblastic leukemia therapy in childhood with a modified BFM protocol in a multicenter study in the German Democratic Republic. Haematol Blood Transfus. 1987; 30:471–9. [PubMed: 3305215]

- 36. Tsurusawa M, Katano N, Yamamoto Y, et al. Improvement in CNS protective treatment in nonhigh-risk childhood acute lymphoblastic leukemia: report from the Japanese Children's Cancer and Leukemia Study Group. Med Pediatr Oncol. 1999; 32:259–6. [PubMed: 10102019]
- 37. Viana MB, Murao M, Ramos G, et al. Malnutrition as a prognostic factor in lymphoblastic leukaemia: a multivariate analysis. Arch Dis Child. 1994; 71:304–10. [PubMed: 7979521]
- Tsuchida M, Ohara A, Manabe A, et al. Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984-1999. Leukemia. 2010; 24:383–96. [PubMed: 20033052]
- Hann I, Vora A, Richards S, et al. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomised trials. UK Medical Research Council's Working Party on Childhood Leukaemia. Leukemia. 2000; 14:356– 63. [PubMed: 10720126]
- Salzer WL, Devidas M, Carroll WL, et al. Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: a report from the children's oncology group. Leukemia. 2010; 24:355–70. [PubMed: 20016527]
- 41. Chessells JM, Durrant J, Hardy RM, Richards S. Medical Research Council leukaemia trial--UKALL V: an attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia. Report to the Council by the Working Party on Leukaemia in Childhood. J Clin Oncol. 1986; 4:1758–64. [PubMed: 3537216]
- Eden OB, Lilleyman JS, Richards S. Testicular irradiation in childhood lymphoblastic leukaemia. Medical Research Council Working Party on Leukemia in Childhoods. Br J Haematol. 1990; 75:496–8. [PubMed: 2207001]
- Brandalise S, Odone V, Pereira W, et al. Treatment results of three consecutive Brazilian cooperative childhood ALL protocols: GBTLI-80, GBTLI-82 and -85. ALL Brazilian Group. Leukemia. 1993; 7(Suppl 2):S142–5. [PubMed: 8361220]
- Tsuchida M, Akatsuka J, Bessho F, et al. Treatment of acute lymphoblastic leukemia in the Tokyo Children's Cancer Study Group--preliminary results of L84-11 protocol. Acta Paediatr Jpn. 1991; 33:522–32. [PubMed: 1792912]
- Duttera MJ, Bleyer WA, Pomeroy TC, et al. Irradiation, methotrexate toxicity, and the treatment of meningeal leukaemia. Lancet. 1973; 2(7831):703–7. [PubMed: 4125793]
- 46. Jones B, Freeman AI, Shuster JJ, et al. Lower incidence of meningeal leukemia when prednisone is replaced by dexamethasone in the treatment of acute lymphocytic leukemia. Med Pediatr Oncol. 1991; 19:269–75. [PubMed: 2056971]
- Komp DM, Fernandez CH, Falletta JM, et al. CNS prophylaxis in acute lymphoblastic leukemia: comparison of two methods a Southwest Oncology Group study. Cancer. 1982; 50:1031–6. [PubMed: 7049344]
- Dritschilo A, Cassady JR, Camitta B, et al. The role of irradiation in central nervous system treatment and prophylaxis for acute lymphoblastic leukemia. Cancer. 1976; 37:2729–35. [PubMed: 1065467]
- Brecher ML, Berger P, Freeman AI, et al. Computerized tomography scan findings in children with acute lymphocytic leukemia treated with three different methods of central nervous system prophylaxis. Cancer. 1985; 56:2430–3. [PubMed: 3862463]
- Ortega JA, Nesbit ME, Sather HN, et al. Long-term evaluation of a CNS prophylaxis trial-treatment comparisons and outcome after CNS relapse in childhood ALL: a report from the Childrens Cancer Study Group. J Clin Oncol. 1987; 5:1646–54. [PubMed: 3309198]
- Steinherz PG, Gaynon PS, Breneman JC, et al. Treatment of patients with acute lymphoblastic leukemia with bulky extramedullary disease and T-cell phenotype or other poor prognostic features: randomized controlled trial from the Children's Cancer Group. Cancer. 1998; 82:600–12. [PubMed: 9452280]
- Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: a CLCG-EORTC report. Children Leukemia Cooperative Group. Leukemia. 2000; 14:2257–66. [PubMed: 11187917]
- 53. Donadieu J, Auclerc MF, Baruchel A, et al. Critical study of prognostic factors in childhood acute lymphoblastic leukaemia: differences in outcome are poorly explained by the most significant

prognostic variables. Fralle group. French Acute Lymphoblastic Leukaemia study group. Br J Haematol. 1998; 102:729–39. [PubMed: 9722300]

- Holland JF, Glidewell O. Chemotherapy of acute lymphocytic leukemia of childhood. Cancer. 1972; 30:1480–7. [PubMed: 4509104]
- Sackmann Muriel F, Pavlovsky S, Penalver JA, et al. Evaluation of induction of remission, intensification, and central nervous system prophylactic treatment in acute lymphoblastic leukemia. Cancer. 1974; 34:418–26. [PubMed: 4527793]
- 56. Moss HA, Nannis ED, Poplack DG. The effects of prophylactic treatment of the central nervous system on the intellectual functioning of children with acute lymphocytic leukemia. Am J Med. 1981; 71:47–52. [PubMed: 6941699]
- Borsi JD, Wesenberg F, Stokland T, Moe PJ. How much is too much? Folinic acid rescue dose in children with acute lymphoblastic leukaemia. European Journal of Cancer. 1991; 27:1006–9. [PubMed: 1832883]
- Skarby TV, Anderson H, Heldrup J, et al. High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. Leukemia. 2006; 20:1955–62. [PubMed: 16990760]
- Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves eventfree survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood. 2011; 118:243–51. [PubMed: 21562038]
- 60. Winick NJ, Salzer WL, Devidas M, Nachman JB. Dexamethasone (DEX) versus prednisone (PRED) during induction for children with high-risk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Onocology Group Study AALL0232. J Clin Oncol. 2011; 29(suppl) abstr 9504.
- 61. Larsen EC, Salzer WL, Devidas M, et al. Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginse (C-MTX/ASNase) in children and young adults with highrisk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Oncology Group Study AALL0232. J Clin Oncol. 2011; 29(suppl) abstr 3.
- 62. Nathan PC, Whitcomb T, Wolters PL, et al. Very high-dose methotrexate (33.6 g/m(2)) as central nervous system preventive therapy for childhood acute lymphoblastic leukemia: results of National Cancer Institute/Children's Cancer Group trials CCG-191P, CCG-134P and CCG-144P. Leuk Lymphoma. 2006; 47:2488–504. [PubMed: 17169794]

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| B) BER-PH3 100 B) BER-PH3 100 B) BER-PH3 101 B) COLL BIS COURS PT7 B) COLL BIS COURS | 102 10317 103 | 2027 8437 84511300 (24.7%) *= 0 6; NS 777 (49.6%) *= 0 6; NS 15/79 22305 15/79 22305 15/79 22305 15/79 224054 (24.5%) *= 0 6; NS 224054 (24.5%) *= 0 6; NS | -0.1 3.3 -18.7 4.2 -0.8 3.0 6.4 -3.1 -3.6 -2.6 6.4 -3.1 -2.6 -4.7 -2.6 -4.8 -1.2 -2.6 -4.8 -4.7 -2.6 -4.8 -4.7 -4.8 -4.8 -4.8 -4.8 -4.8 -4.8 -4.8 -4.8 | 97 437 2193 10-1 5-1 12-9 28-1 60 60 92 53-1 30 11-7 11-7 88-7 | | 1%(2)2 d%(0) 3%(0) 8%(6) reduction 2P = 0.2; NS 40%(0) 2%(2) 2%(2) 40%(0) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) 2%(2) | COLOR OF TOT, THE COLOR OF TOT, THE COLOR OF TOT COLOR COLOR OF TOT COLOR COLOR OF TOT COLOR COLOR OF TOT VIMITATION COLOR OF TOT VIMITATION COLOR OF TOT VIMITATION COLOR OF TOT VIMITATION COLOR OF TOT | 1:1:1:1:1:1:1:1:1:1:1:1:1:1:1:1:1:1:1: | rtz= tit: 238/580 =Control: 220/58 19/44 239/602 (39.7%) 0.1; P = 0.8; 2=IV MTX: 150/286 45/137 34/84 11/40 24/54 30/47 | -2·6 -8·3 0·0 -8·3 NS -4·9 -6·6 4·1 -0·5 -2·0 | 117-7 105-4 9-0 114-4 71-9 20-2 16-1 5-5 11-2 | | | 2% (9) 0% (3) 0% (33) 7% (9) reduction 2P = 0-4; N 7% (11) 20% (19) -29% (23) |
| 80 CC0-1892 0.101 Image: Second | $\begin{array}{c} 3317\\ +1314\\ +353$ | 44/319 45/1920 (14.7%) = 0.6; NS 10/41 13/42 60/121 (49.6%) 15/79 23/84 15/79 23/84 15/79 23/84 13/79 8/44 22/84 13/78 31/78 46/178 23/78 31/78 31/78 31/78 35/79 | 3.3 -18-7 -8-8 3.0 6-4 -3-1 -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 43.7 219-3 10-1 5-1 12-9 28-1 60 92 83-1 30 11-7 11-7 88-7 | | - 4% (8) 8% (8) reduction 2P = 0 2; NS - 42% (20) - 45% (21) 26% (21) - 40% (32) - 40% (32) - 30% (27) 26% (7) | D: MIXHT CITT. TH STRATE CIT. TH STRATE CITE CITE STRATE CITE STRATE CITE STRATE CITE STRATE STRAT | 1=1/2 MTX+11 v 1 233/579 T. Trt1=IT v Trt2 202/534 17/38 219/572 (38.3%) etween trialsX ² ₁ = 1 17/138 : Trt1=CRT v Trt 188/259 36/142 33/70 11/42 21/55 32/55 32/55 | <pre>rtt2= tit1: 238/580 =Control: 220/558 19/44 239/602 (39.7%) 0-1; P = 0-8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54</pre> | -2.6 -8.3 0.0 -8.3 NS -4.9 -6.6 4.1 -0.5 -2.0 | 117-7 105-4 9-0 114-4 71-9 20-2 18-1 5-5 11-2 | | | 2% (9) 0% (33) 7% (9) reduction 2P = 0.4; N 2% (11) 28% (12) -29% (23) |
| Bakeszi: 625 Test for Hencess theory 62 Test for Hencess theory 62 Bakeszi: 62 <td>$\begin{array}{c} 14314\\ .4753$.4753\\ .4753 .4753\\ .4753 .4753 .47532\\ .4753 .4753 .4753 .4753 .4753 .4753 .4753 .4753 .</td> <td>45(11500 (34.7%) = 0.6; NS TTT: 1041 1338 3142 60121 (49.5%) = 0.6; NS 15/79 23/84 150/376 6/64 23/870 23/84 150/376 6/64 23/870 23/84 150/376 24/95 28/100 22/84 15/79 23/84 23/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/78</td> <td>-18-7 4-2 -08 3-0 6-4 -3-1 -3-1 -3-1 -3-1 -3-1 -3-1 -3-1 -3</td> <td>219-3 10-1 5-1 12-9 28-1 6-0 9-2 53-1 3-0 11-7 11-7 88-7</td> <td></td> <td>8% (8) reduction 2P = 0-2; NS </td> <td>E: Addn of IT to CRT+I 78 cCG-162 79 UKALL VII ■ Subtotal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL VII 81 ALL VII 87 JCCLSG L-874 88 GCMTLA 80 UKALL XI HWCC</td> <td>233/5/9 T. Trt1=IT v Trt2 202/534 17/38 219/572 (38.3%) etween trials/?₁ = Trt1=CRT v Trt 138/259 36/142 33/70 11/42 21/55 32/55</td> <td>238/860 =Control: 220/558 19/44 239/602 (39.7%) 0-1; P = 0-8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67</td> <td>-2.6 -8.3 0.0 -8.3 NS -4.9 -6.6 4.1 -0.5 -2.0</td> <td>117-7 9-0 114-4 71-9 20-2 18-1 5-5 11-2</td> <td></td> <td></td> <td>2% (9) 0% (33) 7% (9) reduction 2P = 0.4; N 7% (11) 28% (19) -29% (23)</td> | $\begin{array}{c} 14314\\ .4753$.4753\\ .4753 .4753\\ .4753 .4753 .47532\\ .4753 .4753 .4753 .4753 .4753 .4753 .4753 .4753 . | 45(11500 (34.7%) = 0.6; NS TTT: 1041 1338 3142 60121 (49.5%) = 0.6; NS 15/79 23/84 150/376 6/64 23/870 23/84 150/376 6/64 23/870 23/84 150/376 24/95 28/100 22/84 15/79 23/84 23/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/78 | -18-7 4-2 -08 3-0 6-4 -3-1 -3-1 -3-1 -3-1 -3-1 -3-1 -3-1 -3 | 219-3 10-1 5-1 12-9 28-1 6-0 9-2 53-1 3-0 11-7 11-7 88-7 | | 8% (8) reduction 2P = 0-2; NS | E: Addn of IT to CRT+I 78 cCG-162 79 UKALL VII ■ Subtotal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL VII 81 ALL VII 87 JCCLSG L-874 88 GCMTLA 80 UKALL XI HWCC | 233/5/9 T. Trt1=IT v Trt2 202/534 17/38 219/572 (38.3%) etween trials/? ₁ = Trt1=CRT v Trt 138/259 36/142 33/70 11/42 21/55 32/55 | 238/860 =Control: 220/558 19/44 239/602 (39.7%) 0-1; P = 0-8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -2.6 -8.3 0.0 -8.3 NS -4.9 -6.6 4.1 -0.5 -2.0 | 117-7 9-0 114-4 71-9 20-2 18-1 5-5 11-2 | | | 2% (9) 0% (33) 7% (9) reduction 2P = 0.4; N 7% (11) 28% (19) -29% (23) |
| Test for heterogeneity between these 7.4 Bio (CHT / CHT / C | $X_{3}^{2} = 2.3; P = 0$ 7 rt2=DIT/TTT : (46) (42) (43) (44) (44) (44) (44) (45) (44) (45) | P = 0 €; NS TTT: 10/41 13/38 33/42 60/121 (49.6%) P = 0 6; NS 15/79 23/84 130/376 6/64 27/20 23/84 130/376 6/64 27/20 23/84 130/376 6/64 27/20 23/84 130/376 6/64 27/20 23/84 130/376 6/64 27/20 23/84 130/376 6/64 15/79 23/84 27/20 | 42 -08 30 64 -31 -39 -286 -03 -47 -26 -38-1 | 10-1 5-1 12-9 28-1 60 92 53-1 30 11-7 11-7 88-7 | | 2 = 0.2, (NS (NS (21)) 26% (21) 10% (21) 10% (22) 20% (22) 40% (32) 20% (27) 20% (11) | E: Addin of IT to CRT+I 78 CC5-162 79 UKALL VII Subtotal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL-BFM-81 81 ALL-9FM-81 81 ALL-9FM-81 87 JCCLSG I-874 88 GCMTLA 80 UKALL XI HWCC | T. Trt1=IT v Tr2 202/534 17/38 219/572 (38.3%) etween trialsX ² ₁ = . Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | =Control: 220/558 19/44 239/602 (39.7%) 0-1; P = 0-8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -8:3 0:0 -8:3 NS -4:9 -6:6 4:1 -0:5 -2:0 | 105.4 9.0 114.4 71.9 20.2 16.1 5.5 11.2 | | | 0% (3) 0% (3) 7% (9) reduction 2P = 0-4; N 7% (11) 28% (19) -29% (25) |
| Lease Section 1. 2014. 2014 Lease Section 1. 2014. 2014. Lease Section 1. 2014. 2014. Lease Section 1. 2014. | $\gamma_3 = 2.3$, $p = 0.0$ $\gamma_1 = 2.3$, $p = 0.0$ $\gamma_1 = 1.1$; $p = 0.0$ $\gamma_2 = 1.1$; $p = 0.0$ $\gamma_2 = 1.1$; $p = 0.0$ $\gamma_1 = 1.0$ $\gamma_1 = 1.0$ $\gamma_1 = 0.0$ $\gamma_1 = 0.0$ $\gamma_1 = 0.0$ $\gamma_2 = 1.1$; $p = 0.0$ $\gamma_1 = 0.0$ $\gamma_2 = 1.1$; $p = 0.0$ $\gamma_1 = 0.0$ $\gamma_2 = 1.0$; $p = 0.0$ $\gamma_1 = 0.0$ $\gamma_2 = 1.0$; $p = 0.0$ $\gamma_1 = 0.0$ $\gamma_2 = 1.0$; $p = 0.0$ $\gamma_2 = 1.0$; $\gamma_2 = 1.0$; $\gamma_2 = 1.0$; $\gamma_3 = 1.0$; $\gamma_4 = $ | = 0 6; NS = 0 6; NS = 0 6; NS 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 15/79 23/84 13/376 6/84 27/20 38/20 24/94 (24.5%) 24/97 23/84 13/376 6/84 27/20 24/94 27/20 23/84 15/79 15/79 15 | 42 -08 30 64 -31 -39 -286 -03 -47 -28 -38-1 | 10-1 5-1 12-9 28-1 6-0 9-2 53-1 3-0 11-7 11-7 11-7 88-7 | | - 42% (18) 18% (41) - 38% (21) 26% (21) Increase 2P = 6-2; NS - 40% (22) - 30% (27) 20% (11) | 78 CCG-162 79 UKALL VII ■ Subtotal: Test for heterogeneity b F: CRT+IT vIV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL-BFM-81 81 ALL VII 81 81 JCL SG L-874 85 JCCLSG L-874 88 GCMTLA 80 UKALL XI HWCC | 202/534 17/38 219/572 (38.3%) etween trials∛ ² = : Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | 220/558 19/44 239/602 (39.7%) 0·1; P = 0·8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -8-3 0-0 -8-3 NS -4-9 -6-6 4-1 -0-5 -2-0 | 105-4 9-0 114-4 71-9 20-2 16-1 5-5 11-2 | | | 0% (3) 0% (3) 7% (9) reduction 2P = 0.4; N 7% (11) 28% (19) -29% (23) |
| 72 (M. 77) 72 (M. 77) 74 (M. 77) 200 84 NB 54 200 85 NB 24 (M. 77) 200 85 NB 24 (M. 77) 200 85 NB 24 (M. 77) 200 80 OF 24 (M. 56 00 SR) 97 80 OF 24 (M. 56 00 SR) 97 80 OF 24 (M. 56 00 SR) 97 70 C Addisso of W XY Se bing semificity 500 91 OF 24 (M. 94 (M. 77) C 100 500 91 OF 24 (M. 94 | <pre>X46 227 1/31 1/64 X23_=1-1; P = 0 Trt2=TIT: 77 YCRT+IT: 7/6 W837 0/64 7/0 2251 4/76 W837 6/6 W837 6/6 (2)_5 = 1-1; P = 0 7/0 175</pre> | 1841 1338 3142 60121 (49.5%) ² = 0.6; NS 15779 23/84 15079 23/84 130/376 6/64 224914 (24.5%) ² = 0.6; NS 31/78 40/178 23/178 40/178 23/178 | 42 -08 30 64 -31 -31 -39 -28 -03 -47 -28 - 38-1 | 10-1 5-1 12-9 28-1 6-0 9-2 53-1 3-0 11-7 11-7 88-7 | | - 45% (39) (1% (47) - 35% (37) - 25% (21) increase 2P = 6-2; NS - 40% (32) - 35% (27) - 35% (77) - 35% (17) | Subtcal: Subtcal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 74 JCCLSG L-874 87 JCCLSG L-874 88 GCMTLA 80 UKALL XI HWCC | 219/572 (38.3%) etween trialsX ² = : Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | 239/602 (39.7%) 0·1; P = 0·8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -8-3 NS -4-9 -6-6 4-1 -0-5 -2-0 | 71-9 20-2 16-1 5-5 11-2 | | | 2% (3) 7% (9) reduction 2P = 0.4; N 2% (1) 28% (19) -29% (2) |
| 64 NS 54 0:00 64 NS 54 0:00 65 NSN P16 0:00 61 NSN P16 0:00 62 NSN P16 0:00 63 NSN P16 0:00 64 NSN P17 0:00 64 NSN P17 0:00 64 NSN P17 <t< td=""><td>127 131 144 145</td><td>13/38 31/42 60/121 (49.6%) ** 0.6; NS 15/79 22/84 130/376 6/64 130/376 6/64 27/230 38/100 22/49/14 (24.5%) ** 0.6; NS 31/78 46/178 28/176 28/176</td><td>-08 30 64 -31 -39 -286 -03 -47 -26 -38-1</td><td>5-1 12.9 28-1 60 92 53-1 30 11-7 11-7 88-7</td><td></td><td>10%(37) -26%(37) -26%(21) Increase 2P = 0-2; NS 40%(32) -25%(27) 20%(11)</td><td>Subtotal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG L-874 88 GCMTLA 89 UKALL XI HWCC</td><td>219/572 (38.3%) etween trials%²1 = 7. Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55</td><td>239/602 (39.7%) 0.1; P = 0.8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67</td><td>-8-3 NS -4-9 -6-6 4-1 -0-5 -2-0</td><td>71.9 20.2 16.1 5.5 11.2</td><td></td><td>- </td><td>7% (9) reduction 2P = 0.4; N 7% (11) 28% (19) -29% (28)</td></t<> | 127 131 144 145 | 13/38 31/42 60/121 (49.6%) ** 0.6; NS 15/79 22/84 130/376 6/64 130/376 6/64 27/230 38/100 22/49/14 (24.5%) ** 0.6; NS 31/78 46/178 28/176 28/176 | -08 30 64 -31 -39 -286 -03 -47 -26 -38-1 | 5-1 12.9 28-1 60 92 53-1 30 11-7 11-7 88-7 | | 10%(37) -26%(37) -26%(21) Increase 2P = 0-2; NS 40%(32) -25%(27) 20%(11) | Subtotal: Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG L-874 88 GCMTLA 89 UKALL XI HWCC | 219/572 (38.3%) etween trials% ² 1 = 7. Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | 239/602 (39.7%) 0.1; P = 0.8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -8-3 NS -4-9 -6-6 4-1 -0-5 -2-0 | 71.9 20.2 16.1 5.5 11.2 | | - | 7% (9) reduction 2P = 0.4; N 7% (11) 28% (19) -29% (28) |
| BARLIPIO 249 Bubboli: 277 Trait for homogeneity bubbeen tage: 12 24 Bubboli: 277 Trait for homogeneity bubbeen tage: 12 24 Bubboli: 277 Bubboli: 277 Bubboli: 278 Bubboli: 274 Bubboli: 274 Bubboli: 274 Bubboli: 274 Bubboli: 274 <t< td=""><td>(31 (164 (8%) X²₂ = 1·1; P = 0 Trt2=TTT: (77 (77 (77 (78 (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (77) (78) (77)</td><td>3142 (49.6%) ≥ = 0 6; NS 15/79 23/94 130/376 8/94 27(230 38/100 (24.6%) ≥ = 0 6; NS 31/78 46/178 281/78 281/78</td><td>30 64 -31 -39 -286 -03 -47 -26 -38-1</td><td>12.9 28-1 60 53-1 30 11-7 11-7 88-7</td><td></td><td>-28% (31) -26% (21) increase 2P = 0.2; NS </td><td>Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC</td><td>(30.3 %) etween trials %1 = . Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55</td><td>0.1; P = 0.8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67</td><td>-4-9 -6-6 4-1 -0-5 -2-0</td><td>71-9 20-2 16-1 5-5 11-2</td><td></td><td></td><td>2P = 0.4; N 2% (11) 28% (19) -29% (28)</td></t<> | (31 (164 (8%) X ² ₂ = 1·1; P = 0 Trt2=TTT: (77 (77 (77 (78 (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (78) (77) (78) (77) | 3142 (49.6%) ≥ = 0 6; NS 15/79 23/94 130/376 8/94 27(230 38/100 (24.6%) ≥ = 0 6; NS 31/78 46/178 281/78 281/78 | 30 64 -31 -39 -286 -03 -47 -26 -38-1 | 12.9 28-1 60 53-1 30 11-7 11-7 88-7 | | -28% (31) -26% (21) increase 2P = 0.2; NS | Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | (30.3 %) etween trials %1 = . Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | 0.1; P = 0.8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -4-9 -6-6 4-1 -0-5 -2-0 | 71-9 20-2 16-1 5-5 11-2 | | | 2P = 0.4; N 2% (11) 28% (19) -29% (28) |
| Somoul | xx ² ₂ = 1 · 1; P = 0 Trt2=TTT: r77 VGRT+IT: r76 384 770 2251 r76 8857 r76 8857 r76 176 177 178 179 179 170 170 170 170 170 170 170 170 | (49.6%) (49.6%) (2006, NS 15/79 130/078 8/84 27/20 224/914 (24.5%) 224/914 (24.5%) 224/914 (24.5%) 224/914 (24.5%) 224/914 (24.5%) 231/78 48/178 231/ | -3-1 -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 92 53-1 11-7 11-7 88-7 | | 26% (21) increase 2P = 0-2; NS 40% (32) 50% (27) 30% (11) | Test for heterogeneity b F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | etween trials X ² ₁ = . Trt1=CRT v Trt 138/259 36/142 33/70 11/42 21/55 32/55 | 0-1; P = 0-8; 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -4-9 -6-6 4-1 -0-5 -2-0 | 71-9 20-2 16-1 5-5 11-2 | B | | 7% (11) 28% (19) -29% (28) |
| Text to hatmogeneity between texts - 24 Bec GRT-OT VIT, TH-CETFOOT VIT, CH-CETFOOT VIT, CH-CET | $X_{2}^{2} = 1 \cdot 1; P = 0$ Trt2=TIT: (77 'ICRT+IT: (78 'ICRT+IT: (78 'ICRT+IT: (78 'ICRT+IT: (78 'ICRT+IT: (78 'ICRT+IT: (78 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (76 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77 'ICRT+IT: (77) | 2 = 0 6; NS 15/79 23/84 13/376 6/64 27/230 22/0914 (24.5%) 22/0914 (24.5%) 31/78 46/178 28/691015 | -3-1 -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 9-2 53-1 3-0 11-7 11-7 88-7 | | 40% (32) | F: CRT+IT v IV MTX+IT 76 CLB 7611 81 ALL-8FM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | Trt1=CRT v Tr 138/259 36/142 33/70 11/42 21/55 32/55 | 2=IV MTX: 150/266 45/137 34/84 11/40 24/54 30/67 | -4·9 -6·6 4·1 -0·5 -2·0 | 71-9 20-2 16-1 5-5 11-2 | | - | 7% (11) 28% (19) -29% (28) |
| Tart for hereingeneting between Tess. 23 BE COT ALL 19: COT 1 | $X_{2}^{2} = 1 \cdot 1; P = 0$ Trt2=TTT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: IVCRT+IT: I | 22/94 15/79 22/94 130/376 8/64 27/230 38/160 224/914 (24.9%) ≥ 0 0; NS 31/78 46/178 281/759 38/1015 | -31 -39 -266 -03 -47 -26 -38-1 | 92 53-1 30 11-7 11-7 88-7 | | - 40% (32) - 35% (27) 39% (11) | 76 CLB 7611 81 ALL-BFM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | 138/259 36/142 33/70 11/42 21/55 32/55 | 150/266 45/137 34/84 11/40 24/54 30/57 | -4·9 -6·6 4·1 -0·5 -2·0 | 71.9 20.2 16.1 5.5 11.2 | | - | 7% (11) 28% (19) -29% (28) |
| Be CRT-01 TT. TH-CRT-01 TT. C-Addisin of IV ITX to brig derm ITC C-Addisin of IV ITX to brig derm ITC C-Addisin of IV ITX to brig derm ITC C-Addisin of IV ITX to brig derm ITC C-ATT. TH-TH VIX to brig derm ITC D-ADDISING to C-ADDISING D-ADDISING to C-ADDISING to C-ADDISING D-ADDISING to C-ADDI | Trt2=TIT: (77 T/CRT+IT: (78 394 394 2251 (76 18537 (76 18537 (76 1954) (70 175 175 175 175 175 177 177 177 | 23/84 130/376 6/64 27/230 38/160 224/914 (24.5%) 24.5%) 26.0 €; NS 31/78 46/178 281/75 281/75 | -3-1 -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 92 53-1 30 11-7 11-7 88-7 | | - 35% (27) 30% (11) | 81 ALL-BFM-81 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | 36/142 33/70 11/42 21/55 32/55 | 45/137 34/84 11/40 24/54 30/57 | -6·6 4·1 -0·5 -2·0 | 20-2 16-1 5-5 11-2 | | • | 28% (19) |
| CA delise of M IXX to be general for CA delise of M IXX to be general for Solution of M IXX to be general solution of M IXX to be general solution solution of M IXX to be general solution of M IXX to be general solution solution o | 777 776 384 776 3854 770 1251 778 18837 .5%) 778 175 770 175 .5% | 15/79 23/94 130/378 6/64 27/230 38/164 224/94 (24.5%) 224/94 (24.5%) 224/94 (24.5%) 31/78 48/178 28/1759 358/1015 | -3-1 -3-9 -2-8-6 -0-3 -4-7 -2-8 -38-1 | 92 53-1 30 11-7 11-7 88-7 | - | 40% (32) - 35% (27) 39% (11) | 81 ALL VII 81 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | 33/70 11/42 21/55 32/55 | 34/84 11/40 24/54 30/57 | 4·1 -0·5 -2·0 | 16-1 5-5 11-2 | | • | -29% (28) |
| C: Addision of V MTX to bing semi Tifk Car TTP, TIFL1 MTX, To Fuedancia Source State | r/CRT+IT: 1/76 3654 770 1251 1/76 10837 .5%) χ ² ₄ = 1-1; P = 0 175 175 | 23/04 130/376 6/64 27/230 38/160 224/914 (24.5%) P = 0.9; NS 31/78 46/178 281/759 358/1015 | -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 9-2 53-1 3-0 11-7 11-7 88-7 | - | - 35% (27) 39% (11) | 87 JCCLSG L-874 87 JCCLSG I-874 88 GCMTLA 90 UKALL XI HWCC | 21/55 32/55 | 24/54 | -2.0 | 11-2 | | | |
| C. Addition of M MIX to bag during the C. Addition of M MIX to bag during the SciEnce Tossue, SciEnce SciEnce Tossue, SciEnce SciEn | ricRT+IT: 1/76 1/364 1/251 1/76 1/25 1/76 1/75 1/75 1/75 1/75 | 23/84 130/376 6/64 27/230 38/160 224/914 (24.5%) P = 0.9; NS 31/78 46/178 281/055 | -3-9 -26-6 -0-3 -4-7 -2-6 -38-1 | 9-2 53-1 3-0 11-7 11-7 88-7 | - | - 35% (27) 39% (11) | 88 GCMTLA 90 UKALL XI HWCC | 32/55 | 30/67 | | | | | 9% (41) |
| 9 SUGHT GENAMA 9 SUGHT GENAMA 9 SUGHT GENAMA 9 FALLE 9 IN 9 FALE 9 IN 9 FALLE 9 IN 9 FALLE 9 IN 9 FALLE 9 IN 9 FALLE 9 I | 1776 1364 170 1251 1776 8%37 5%3) χ ² ₄ = 1−1; P = 0 175 175 | 23/84 130/376 6/64 27/230 38/160 224/914 (24.5%) * = 0.9; NS 31/78 46/178 281/759 358/1015 | -39 -266 -03 -47 -26 -38-1 | 9.2 53.1 3.0 11.7 11.7 88.7 | | - 36% (27) 39% (11) | 90 UKALL XI HWCC | | 30/5/ | 2'0 | 15-4 | | | 10% (27) |
| 92/00 6005/LINE 1 8330 92/00 6005/LINE 1 977 93 50-001 978 93 50-001 978 93 50-001 978 93 50-001 978 93 50-001 978 94 50-001 978 95 50-001 978 | /364 /70 /251 /76 8637 .5%) X ² ₄ = 1−1; P = 0 /70 175 .5% | 130/376 6/64 27/230 38/160 224/914 (24.5%) P = 0.9; NS 31/78 46/178 281/759 358/1015 | -28-6 -03 -4-7 -2-6 -38-1 | 53-1 3-0 11-7 11-7 88-7 | | 39% (11) | | 76/155 | 81/158 | -2.4 | 39-2 | | | 6% (15) |
| 001902.LL 20 UNC 001902.LL 20 UNC 001902.LL 20 UNC 1507 Substant fax XXXX 1568 Substant fax XXXX 1578 Substant fax XXXXX 1578 Substant fax XXXXXX 1578 Substant fax XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | 1251 1251 1276 8837 .6% χ²₄ = 1-1; P = 0 175 175 | 27/230 38/160 224/914 (24.5%) > = 0.9; NS 31/78 48/178 281/759 358/1015 | -4-7 -2-6 -38-1 | 11-7 11-7 88-7 | | | 97 MRC ALL 97 CNS | 8/31 | 8/30 | -0.2 | 4.0 | | | 11% (47) |
| 94 SUCH FIGURA 2016 15.7 | 5/76 5/76 5%) χ ² ₄ = 1·1; P = 0 70 175 75 | 38/160 224/914 (24.5%) > = 0.9; NS 31/78 46/178 281/759 358/1015 | -2-6 -38-1 | 11-7 88-7 | | 10% (55) | Subtotal | 355/809 | 383/826 | -10-0 | 183-5 | <15 | | 5% (7) |
| biocost: 0145 1045 | 8837 8%) x ² ₄ = 1·1; P = 0 175 175 | 224/914 (24.5%) P = 0.9; NS 31/78 46/178 281/759 358/1015 | -38-1 | 88-7 | | 20% (26) | | (43.9%) | (46.4%) | | | 1 | | reduction |
| Test for heterogeneity below test funct. 20 Cor, IT, Trink MT, Y Trink Consect. 303 # 2009 and 2000 307 # 2009 and 2000 303 # 2009 and 2000 303 # 3000 and 2000 303 Test for heterogeneity belower tests. 303 Test for heterogeneity belower tests. 71 Wey start year. E Uby | χ ² ₄ = 1·1; P = 0 170 175 | (24.0%) P = 0.9; NS 31/78 46/178 281/759 358/1015 | | | \Leftrightarrow | 35% (9) | | | | | | | | ∠r = 0·5; N |
| Tarl for heterogeneity between thiss. "2 41 COL 11, Tell + UM 12, Tarl Councel 41 COL 12, Tarl + UM 12, Tarl Councel 41 COL 12, Tarl + UM 12, Tarl + Tard | χ ² ₄ = 1 1; P = 0 (70) 175 | 2 = 0.9; NS 31/78 46/178 281/759 358/1015 | | | | 2P = 0.00005 | Test for heterogeneity b | etween trials%5 = | 4·0; P = 0·8; | NS | | | | |
| Chi (T). THIN' MTX / THIC-Center B COLL 30 307 PT COLL 30 207 PT COLL 30 | 170 | 31/78 46/178 281/759 358/1015 | | | | | G: Higher dose of IV M | ITX. Trt1=Higher | dose: | | | | | |
| 40 Decision 300 40 Decision 300 50 UKUL X1 UNCC 2447 50 UKUL X1 UNCC 710 50 UKUL X1 UNCC 1211 100 UKU X1 1212 101 UKU X1 1212 101 UKU X1 1212 | 175 | 31/78 46/178 281/759 358/1015 | | | | | 94 POG 9405 | 27/141 | 32/144 | -2.0 | 14-5 | | | 13% (25) |
| 90 UKUL XI LVOC 2447 Bobesti: 3033 Tet för härensensky skalenen tikke, 13 3033 Tet för härensensky skalenen tikke, 13 3045 Tet för härense av skalensen tikke, 147 1111 Bilger det det det skalense tikke, 147 1111 Bilger det det det skalense tikke, 147 1111 Bilger det det det skalense tikke, 147 1111 Bilger det det skalense tikke, 147 1111 Bilger det skalense det skalense tikke 1111 Bilger det skalense det skalense det skalense tikke 1111 Bilger det skalense det skalense tikke 1111 Bilger det skalense det skalense tikke 1111 Bilger det skalense | | 281/759 | -3-1 | 15.2 | | -11%(27) | 94 POG 9406 | 116/389 | 128/397 | -3-7 | 61-0 | _ | | 6% (12) |
| bokenski 2013 2013 2014 | 2754 | 358/1015 | -10.7 | 136-2 | | 8% (8) | Subtotal: | 143/530 | 160/541 | -5-8 | 75-5 | \triangleleft | > | 7% (11) |
| | 1999 | | .12-3 | 172-6 | ~ | 7% (7) | | (21.076) | (20.076) | | | | | 2P = 0.5; N |
| Tea to harmogenery between two: -27 '95% Ci for total and substates, 6% Ci for budy start year.' EF 1% Development of the second sec | .3%) | (35.3%) | | | | reduction | Test for heterogeneity b | etween trials%1 = | 0·1; P = 0·8; | NS | | | | |
| Notes Ten 100 drift and and 100 drift 100 drift 100 drift | | | | | better be | tter | | | | | | | | |
| ord and noise T.11 Higher dose, RT, Tictlelljeer dose, RV, Tictlelljeer dose, RV, Tictlelljeer dose, RV, NO, SA, SA, SA, SA, SA, SA, SA, SA, SA, SA | Events/Patient | lients | C | stics | OR ACI. | Odds Redo | | | | | | | | |
| BigBer dock (T): Througher dock 100000 BigBer dock 20000 BigBer dock 200000 BigBer dock 200000 BigBer dock 2000000 BigBer dock 2000000 BigBer dock 2000000000000000000000000000000000000 | 1 | Trt 2 | (0-E) | Var. | (Trt 1 : Trt 2) | (SD) | | | | | | | | |
| BURALIVINO 2042 BURALIVINO 1013 BURALIVINO 1013 BURALIVINO 1013 BURALIVINO 2047 TICLSS (LIL IN) 1014 BURALIVINO 2047 BURALIVINO 2047 BURALIVINO 2047 BURALIVINO 2047 BURALIVINO 2047 BURALIVINO 2047 BURALIVINO 4016 DICCO-101 4016 Soldensider 10722 BURALIVINO 4009 Soldensider 10722 BURALIVINO 4009 Soldensider 3049 BURALIVINO 3049 BURALIVINO <td>85 1</td> <td>109/183</td> <td>1.7</td> <td>55.2</td> <td>_</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> | 85 1 | 109/183 | 1.7 | 55.2 | _ | | | | | | | | | |
| UKALLYIN 1013 UKALLYIN 1706 OBTLAD 2847 UKALLYIN 1706 OBTLAD 2847 UKALSHARA 2847 StateSharA 2847 StateSharA 2847 UKALSHARA 2847 UKALSHARA 2847 UKALSHARA 2847 UKALSHARA 486 UKALSHARA 4386 UKALSHARA 4386 UKALSHARA 4386 Statestat: 1972 UKALSHARA 3403 Statestat: 3403 UKALSHARA 3468 Statestat: 3493 Statestat: 3493 Statestat: 3493 Statestat: 3693 Higher doss // MTX v move HIGHT. 1665 /s) | 2 | 31/45 | -2-5 | 13-9 | | -3% (14) | | | | | | | | |
| Solution Solution TUSS (18-16) 1940 Solution 2947 Solution 2948 Solution 2949 Solution 2949 Solution 2949 Solution 2949 Solution 2949 Solution 2949 Solution 4949 Solution 4949 Solution 4949 Solution 4949 Solution 4949 Solution 4949 Solution 3409 Solution 3493 Solution 3493 Nature dose N WIX v more TIGUT. 3493 | 3 | 23/30 | -1-0 | 7.3 | | 13% (35) | | | | | | | | |
| TICLSG Last-00 1944 TICLSG Last-00 1944 Substatic 22471 Substatic 23471 Substatic 25474 Addition of CKT : 2476 TOTATICAT VTCConsult 2070 COCO-101 4495 Substatic 1972 Substatic 3403 Substatic 3403 Substatic 3403 Substatic 3403 Buildiget abset // MITX unover ITICUT. | 9 | 19/43 33/49 | -2:9 | 9-0 | | 0% (33) | | | | | | | | |
| Subset: 224-07 Subset: 224-07 Subset: 224-07 Subset: 224-07 Subset: 224-07 Subset: 244-07 Subset: 197 Subset: 1972 Subset: 3493 Subset: 3493 Subset: 3493 Higher dose N WITX v more TIGUT: 1972 | .0 | 15/46 | 4.1 | 8.0 | | 17% (23) | | | | | | | | |
| Subtrait: 22420/ 1835 act for heterogravity between traits: 12 Addition of CKT : 12 TO THATERY TWATS-some- 2005-142 4386 Subtrait: 10742 Subtrait: 10742 Ext for heterogravity between traits: 12 Ext for heterogravity between traits: 12 Ext for heterogravity between traits: 13 IN MTKYT THAT-GRT TWATS- BERTOT SINGS: 3493 Subtrait: 3493 Subtrait: 3493 Subtrait: 3493 Higher dose // MITX remove THOTA: 12 | 1 : | 25/72 | -0-9 | 12-0 | - | 7% (28) | | | | | | | | |
| est for heterogravity between traits: 2 / Addition of CRT : :::::::::::::::::::::::::::::::::::: | 37 2 %) (* | 255/468 (54.5%) | -1-6 | 120-8 | \Leftrightarrow | 1% (9) reduction | | | | | | | | |
| Addition of CTT: 120 ThTICFGT Yard-Construit 2000-101 64163 Subharat: 1970/2014 Subharat: 1970/2014 ext for heterogreenly between train: 12 CV MITKIT THTICFGT YHTCGCenterity: 3403 Subharat: 3403 Subharat: 3403 Subharat: 3403 Subharat: 3403 Higher dose // MITX v move TI/CT/: 3403 | χ ₆ ² = 3 3; P = 0 | = 0.8; NS | | | | 2P = 0-9; NS | | | | | | | | |
| EIT TTIT-CRT VT2-Centrol: 20C6-101 64158 3 C0C123 4395 Subtotal: 107242 est for heterogeneity between traise. 72 VE MTXHT TTI-CRT V Tr2-Control: 3493 Subtotal: 3493 Higher dose IV MTX v more IT/DTL: 1000000000000000000000000000000000000 | | | | | | | | | | | | | | |
| COLOR C | 6A . | 07/140 | -17.0 | 27.3 | | | | | | | | | | |
| Subtotal: 1077424 (42%) 442% est for heterogeneity between tals: 7 % WMTX+TT -Trt1=CRT v Trt2=Centro 3 EORTC 5892 Subtotal: 4499 449 449 449 449 449 449 449 449 44 | ~ i | 48/84 | -50 | 22.7 | | 38% (13) | | | | | | | | |
| (44.3%) est for heterogeneity between trais: 73 ex MTX+TT+Trt+CRT v Trd=Centrel: 9 EORT 0 58532 34493 Subtotal: 3449 (8.6%) Higher dose IV MTX v more IT/DT.: | 42 4 | 135/233 | -22-9 | 60-0 | | 32% (11) | | | | | | | | |
| est for heterogeneity between trials: 22 :: IV MTX+IT+ Trt1=CRT v Trt2=Control: 34/93 10: ECRT:: 58/32 34/93 - Subtotal: 34/93 (6.6.%) Higher dose IV MTX v more IT/DIT.: | %) (5 | (57.9%) | | | | reduction | | | | | | | | |
| (IV MTX+IT+Trt=CRT v Trt2=Contol: ECRTC 5882 Subtotal: 34/93 (96.6%) Higher dose IV MTX v more IT/DIT.: | X2=09 P=0 | = 0.3: NS | | | | 2P = 0.003 | | | | | | | | |
| vr m.A*IIT ITIN=VKI V ITZ2Control: seORTC 5832 34/93 Subtotal: 34/93 (86.6%) Higher dose IV MTX v more IT/DIT.: | | 50,00 | | | | | | | | | | | | |
| Subtotal: 34/93 (36.6%) Higher dose IV MTX v more IT/DIT.: | 1: (3 | 33/96 | 1.7 | 16-7 | | | | | | | | | | |
| (36.6%) Higher dose IV MTX v more IT/DIT.: | a | 33/96 | 1.7 | 16-7 | | -11% (20) | | | | | | | | |
| Higher dose IV MTX v more IT/DIT.: | ×) (| (34.4%) | | | | 11% (26) increase 2P = 0-7; NS | | | | | | | | |
| - | | | | | | | | | | | | | | |
| rt1=IV MTX v Trt2=IT/DIT: | | | | | | | | | | | | | | |
| 7 FRALLE 87 LR 35/63 | | 72/125 | -0.2 | 23.6 | | 1% (20) | | | | | | | | |
| 110/258 | 3 7 | 108/254 | U-4 | 046 | | -1% (14) | | | | | | | | |
| Subtotal: 145/321 (45.2%) | 3 7 58 1 | 180/379 (47.5%) | 0-2 | 78-1 | \sim | 0% (11) reduction 2P = 1.0: NS | | | | | | | | |
| est for heterogeneity between trials: χ^2_2 | 3 7 58 1 21 1 %) (9 | = 0.9; NS | | | | | | | | | | | | |
| Addn of IV MTX+IT/DIT/TIT to CRT+IT/ | 3 7 58 1 21 1 %) θ χ ² ₁ =00;P=0 | TX: | | | | | | | | | | | | |
| rt1=IV MTX+IT,DIT,TIT v Trt2=Control: | 13 58 1 21 1 %) (P = 0 7/1117/V MTX- | | | | | | | | | | | | | |
| ALL VII 81 14/43 | 13 1 58 1 %) (P X ² ₁ = 0 0; P = 0 1/TTT/IV MTX: | 1345 | 0.4 | 6.8 | | -6% (40) | | | | | | | | |
| FTCCSG L84-11 SN 18/92 FTCCSG L84-11 HR 44/113 | 13 1 58 1 21 1 %) θ χξ=00; P=0 τητηγν MTX: 3 | 28/95 | -5°2 4:9 | 20.7 | | 37% (24) | | | | | | | | |
| Subtotal: 700.00 | 13 1 158 1 21 1 121 1 1 121 1 121 1 | and a shall | 0.4 | 38.4 | | -27% (25) | | | | | | | | |
| Juneotai: 76/248 (30.6%) | 13 158 1 21 1 3 2 3 3 2 3 3 | 00/262 | 0.1 | 20.4 | | reduction 2P = 1.0: NP | | | | | | | | |
| est for heterogeneity between trials: | 53 1 56 1 21 1 %) θ χ ² ₁ = 0 0; P = 0 Γ/ΤΤΤ/V MTX: 3 2 : 13 3 18 8 %) (5 | 80/263 (30.4%) | | | | AF - 10; NS | | | | | | | | |
| 5% CI for total and subtotals, 99% CI for ir | 13 1 158 1 14 1 14 1 14 1 14 1 14 1 14 1 15 1 14 1 15 | 80/263 (30.4%) = 0.2; NS | | | | 5 22 | | | | | | | | |
| | 13 158 1 121 1 158 1 1717 1 1 | 80/263 (30.4%) P = 0.2; NS trials | | 00 | Trt 1 T | 12 | | | | | | | | |

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.



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 therap | ý | | |
| *CCG-1952 | 1996 | Π | $DITa \times 1 + IT MTX \times 1 \text{ R}: TITa \times 14 \text{ (f) or } 18 \text{ (m) } \text{ v IT } MTX \times 14 \text{ (f) or } 18 \text{ (m)}$ |
| B: Radiotherapy plus II | therapy | versu | extra IT therapy |
| a Radiotherapy v IT thera | ЪХ | | |
| CCG-161 | 1978 | 12 | IT MTX \times 6 R: 18 Gy CRT v IT MTX \times 8 |
| CCG-105 | 1983 | 13 | IT MTX \times 6 R: 18 Gy CRT v IT MTX \times 8 (f) or 14 (m) |
| INEN-P83 | 1983 | | IT MTX \times 5 R: 18 Gy CRT v IT MTX \times 12 |
| CCG-1882 | 1989 | 14 | IT MTX \times 14 (f) or 18 (m) + IT AraC \times 1 R: 18 Gy CRT v IT MTX \times 7 |
| <u>b</u> Radiotherapy (+ IT) v E | OIT or TI | T thera | x |
| †SWOG 7623/AlinC12 | 1976 | 15 | R: 24 Gy CRT + IT MTX \times 5 v TITa \times 22 |
| LAL 7/78 | 1978 | 16 | R: 24 Gy CRT + IT MTX \times 6 v DITa \times 10 |
| INS 84 | 1984 | 17 | TITa × 6 R: 18Gy CRT v TITa × 12 |
| INEN-P85 | 1985 | | R: 18 Gy CRT + IT MTX \times 5 v TITa \times 17 |
| c Radiotherapy + DIT v T | IT therag | X | |
| [*] DFCI ALL 95-001 | 1996 | 18 | IT AraC \times 1 + TITa \times 2 R: 18Gy CRT + DITa \times 6 v TITa \times 12 |
| C: Addition of IV metho | trexate 1 | to long | term IT therapy or radiotherapy with IT therapy |
| a TIT therapy +/- IV meth | otrexate | | |
| SJCRH Total XIIIA | 1991 | 19 | TITa \times 13 or 17 + 2 g/m^2IV MTX \times 9 or 10 R: \pm 1 g/m² IV MTX \times 1 |
| *POG 9005 | 1991 | 20 | 1 g/m² IV mp \times 17–19 + TITA \times 16 R: \pm 1 g/m² IV MTX \times 12 |
| FRALLE 93 LR | 1993 | 21 | TITC × 16 R: \pm 1.5 g/m ² IV MTX × 6 |
| FRALLE 93 IR | 1993 | 21 | TITC \times 18 R: \pm 8 g/m ² IV MTX \times 4 |
| *SJCRH Total XIIIB | 1994 | 22 | $1~g/m^2~IV~mp+TITa \times 13~or~15+2~g/m^2~IV~MTX \times 10~R:\pm 1~g/m^2~IV~MTX \times 1$ |
| b IT therapy +/- IV metho | otrexate | | |
| CCG-139 | 1984 | 23 | IT MTX \times 15 (f) or 20 (m) R: \pm 0.5 g/m² IV MTX \times 24 (f) or 33 (m) |
| DFCI 87001 | 1987 | 24 | IT AraC \times 1 + IT MTX \times 10 (HR: + 18 Gy CRT) R: \pm 4 g/m² IV MTX \times 1 |
| UKALLXI LWCC | 1990 | 25 | IT MTX \times 16 R: \pm 6–8 g/m² IV MTX \times 3 |
| c Radiotherapy with IT th | erapy +/- | IV me | thotrexate |

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| Trial | Year | Ref | CNS-directed therapy |
|---------------------------|------------|---------|---|
| DFCI 81001 | 1981 | 26 | 18 or 28 Gy CSCRT + IT AraC \times 1 + IT MTX \times 8 R: \pm 4 g/m²IV MTX \times 1 |
| *POG 9404 | 1994 | 27 | TITa \times 11 + 18 Gy CRT R: \pm 5 g/m^2 IV MTX \times 4 |
| D: IV methotrexate + IT | therapy | ' v TIT | |
| [*] POG8035/8036 | 1981 | 28 | TITa \times 6 R: 1 g/m² IV MTX \times 17 + IT MTX \times 4 v TITa \times 17 |
| E: Addition of IT therap | oy to radi | iothera | y plus short-term IT therapy |
| [†] CALGB-7113 | 1971 | 29 | 24 Gy CRT + IT MTX × 12 R: \pm IT MTX × 3 |
| CCG-162 | 1978 | 30 | 18 Gy CRT + IT MTX \times 6 R: \pm IT MTX \times 8 |
| UKALLVII | 1979 | 31 | 18 or 24 Gy CRT + IT MTX \times 5 R: \pm IT MTX \times 8 |
| F: Radiotherapy plus II | therapy | v IV m | ethotrexate plus IT therapy |
| CLB 7611 | 1976 | 32 | IT MTX \times 6 R: 24 Gy CRT v 0.5 g/m² IV MTX \times 3 |
| ŕNCI 77-02 | 1980 | 33 | R: 18–24 Gy CRT + IT MTX \times 5 v 33.6 g/m² IV MTX \times 10 |
| ALL-BFM-81 | 1981 | 34 | IT MTX \times 6 R: 12–18 Gy CRT v 0.5 g/m² IV MTX \times 4 |
| Jena ALL VII 81 | 1981 | 35 | IT MTX \times 8 R: 18 Gy CRT v 0.5 g/m² IV MTX \times 4 |
| JCCLSG L-874 | 1987 | 36 | DITb \times 3 R: 18 Gy CRT v 2 g/m^2 IV MTX \times 3 + DITb \times 6 |
| JCCLSG I-874 | 1987 | 36 | $(2~g/m^2\times1+4.5~g/m^2\times20)~IV~MTX+DITb\times1~R; 18~Gy~CRT+DITb\times2~v~4.5~g/m^2~IV~MTX\times3$ |
| GCMTLA | 1988 | 37 | TITb \times 6 R: 12–18 Gy CRT v 0.5 g/m² IV MTX \times 4 + TITb \times 6 |
| ŕTCCSG L89-12 | 1989 | 38 | TITa \times 4 + DITa \times 3 R: 18 Gy CRT v 3 g/m² IV MTX |
| UKALLXI HWCC | 1990 | 25 | IT MTX \times 7 or 9 R: 24 Gy CRT v 6–8 g/m² IV MTX \times 3 + IT MTX \times 8 or 9 |
| ŕTCCSG L92-13 HR | 1992 | 38 | DITb \times 4 + TITa \times 3 R: 18 Gy CRT + DITb \times 1 v 3 g/m² IV MTX \times 2 |
| *MRC ALL97 | 1997 | 39 | IT MTX \times 7 or 9 R: 24 Gy CRT v 6–8 g/m² IV MTX \times 3 + IT MTX \times 8 or 9 |
| G: Higher dose of IV me | ethotrexa | ıte | |
| *POG 9405 | 1994 | 40 | TITa \times 22 R: 2.5 g/m² IV MTX \times 12 v 1 g/m² IV MTX \times 12 |
| *POG 9406 | 1994 | 40 | TITa \times 18 + 1 g/m² IV mp \times 6 R: 2.5 g/m² IV MTX \times 6 v 1 g/m² IV MTX \times 6 |
| H: Higher doses of radic | otherapy | | |
| UKALL V | 1976 | 41 | IT MTX \times 5 R: 24 Gy v 21 Gy CRT |
| UKALLVI(i) | 1978 | 42 | IT MTX \times 8 or IT MTX \times 6 + IT AraC \times 2 + 0.5 g/m² IV MTX \times 3 R: 24 Gy v 21 Gy CRT |
| UKALLVI(ii) | 1978 | 42 | IT MTX \times 8 or IT MTX \times 6 + IT AraC \times 2 + 0.5 g/m² IV MTX \times 3 R: 24 Gy v 18 Gy CRT |
| UKALLVII | 1979 | 31 | IT MTX \times 5 R: 24 Gy v 18 Gy CRT |
| GBTLI-80 | 1980 | 43 | IT MTX \times 13 R: 24 Gy v 18 Gy CRT |
| | | | |

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| Trial | Year | Ref | CNS-directed therapy |
|-----------------------------------|----------|---------|---|
| TCCSG L81-10 | 1981 | 44 | DfTa×5 R: 24 Gy v 18 Gy CRT |
| ALL-BFM-83 | 1983 | 34 | IT MTX \times 8 + 0.5 g/m^2 IV MTX \times 4 R: 18 Gy v 12 Gy CRT |
| I: Addition of radiothera | py | | |
| a Addition to IT | | | |
| [†] POG CNS2 | 1970 | 45 | IT MTX \times 20 R: \pm 24 Gy CRT |
| ŕCLB 7111 | 1971 | 46 | IT MTX \times 6 R: \pm 24 Gy CRT |
| [†] SWOG 690/691/Alinc9 | 1971 | 47 | $TTTa \times 10 \text{ R}: \pm 18-24 \text{ Gy CRT}$ |
| [↑] DFCI-SFCC | 1972 | 48 | IT MTX \times 9 R: \pm 24 Gy CRT |
| $ m \red{p}$ CLB 7411 | 1974 | 49 | IT MTX \times 6 R: \pm 24 Gy CRT |
| CCG-101 | 1974 | 50 | IT MTX \times 6 R: \pm 24 Gy CRT |
| *CCG-123 | 1983 | 51 | IT AraC × 1 + IT MTX × 6 R: \pm 18Gy CRT |
| <u>b</u> Addition to IV with IT | | | |
| EORTC 58832 | 1983 | 52 | $2.5 \text{ g/m}^2 \text{ IV MTX} \times 4 + \text{IT MTX} \times 7 \text{ R}$: $\pm 16-20 \text{ Gy CRT}$ |
| J: Higher dose of IV met | otrexat | ie v mo | e IT or DIT therapy |
| FRALLE 87 | 1987 | 53 | DITc \times 5 R: 8 g/m ² IV MTX \times 4 v 3 g/m ² IV MTX \times 4 + DITc \times 5 |
| FRALLE 89 | 1989 | 21 | IT MTX \times 5 R: 8 g/m²IV MTX \times 4 v 3 g/m²IV MTX \times 4 + IT MTX \times 5 |
| K: Addition of IV metho | rexate p | olus 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 \times 8 R: \pm 0.5 g/m^2 IV MTX \times 4 + IT MTX \times 4 |
| TCCSG L84-11 SR | 1984 | 38 | $18~\mathrm{Gy~CRT} + \mathrm{TITa} \times 5 + 0.5~\mathrm{g/m^2~IV~MTX} \times 4 + \mathrm{IT~MTX} \times 4 \mathrm{R}: \pm 0.5~\mathrm{g/m^2~IV~MTX} \times 3 + \mathrm{DITb} \times 6 \mathrm{MTX} \times 3 + \mathrm{DITb} \times 6 \mathrm{MTX} \times 3 + \mathrm{DITD} \times 3$ |
| TCCSG L84-11 HR | 1984 | 38 | $24~Gy~CRT + TITa \times 5 + 0.5g/m^2~IV~MTX \times 12 + DITb \times 12~R; \pm 0.5~g/m^2~IV~MTX \times 3 + TITa \times 6$ |
| Other comparisons with | ut data | | |
| $\dot{	au}$ ALGB 6801 | 1968 | 54 | R: IT MTX × 15 |
| ŕGATLA-70 | 1970 | 55 | $R:\pm 24~Gy~CRT+IT~MTX 	imes 5$ |
| ŕNCI 72-1 | 1971 | 56 | 24 Gy CRT R: IT AraC \times 38 v IT MTX \times 35 |
| ŕNCI-84-C-153A | 1984 | | R: 33-6 g/m^2 IV MTX \times 10 v IT MTX \times 8 |
| \dot{f}^{t} Data not available; | | | |

dexamethasone; f, female; Hc, hydrocortisone; IT, intrathecal; m, male; mp, mercaptopurine; MTX, methotrexate; P, prednisone; R, randomization; TTTa, IT MTX + IT AraC + IT Hc; TTFb, IT MTX + IT AraC + IT P.

* 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,

| Summary results | | | Table II | |
|---------------------------------|--|-------------------------------|------------------------------|---|
| Trial | Background CNS treatment | Arm 1 | Arm 2* | Conclusions |
| A: TIT versus IT the | rapy (n=2029) | | | |
| CCG-1952 ¹¹ | $DIT \times 1 + IT \times 1$ | $TIT \times 14$ (f) or 18 (m) | IT \times 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 plu | is short-term IT therapy versus extra] | IT therapy (n=2614) | | |
| CCG-161 ¹² | $\mathrm{IT} \times 6$ | CRT | $\mathrm{IT} 	imes 8$ | Adding CRT to short-term IT reduced CNS relapses (OR=0.68; p=0.01) compared |
| CCG-105 ¹³ | $\Pi \times 6$ | CRT | IT \times 8 (f) or 14 (m) | with adding more 11 doses, but did not substantially affect EFS ($OR=0.92$; 95% $CI = 0.80 \cdot 1.05$; $p=0.2$). |
| INEN-P83 | $IT \times 5$ | CRT | $IT \times 12$ | |
| CCG-1882 ¹⁴ | $\mathrm{TT} 	imes 15$ (f) or 19 (m) | CRT | IT 	imes 7 | |
| Bb: Radiotherapy plu | is short-term IT therapy versus DIT o | r TIT (n=234) | | |
| LAL 7/78 ¹⁶ | | $CRT + IT \times 6$ | $DIT \times 10$ | Small numbers make results uncertain but OS was worse with CRT (OR=1.63; |
| INS 84 ¹⁷ | $TTX \times 6$ | CRT | $\mathrm{TIT} 	imes 12$ | D-0-02 |
| INEN-P85 | | $CRT + IT \times 5$ | $TIT \times 17$ | |
| Bc: Radiotherapy plu | is DIT versus extra TIT (n=155) | | | |
| DFCI ALL 95-001 ¹⁸ | $TT \times 1 + TTT \times 2$ | $CRT + DIT \times 6$ | $TIT \times 12$ | Insufficient data to draw any conclusions. |
| Ca: Addition of IV m | ethotrexate to TIT or TIT with IV met | thotrexate (n=1751) | | |
| SJCRH Total XIIIA ¹⁹ | TIT \times 13 or 17 + IV \times 9 or 10 | $\mathrm{IV}\times 1$ | Control | Adding IV MTX to TIT reduced both CNS (OR=0-48; p=0-0009) and non-CNS |
| POG 9005 ²⁰ | IV mp \times 17–19 + TIT \times 16 | IV 	imes 12 | Control | relapse (UK=0.65; p=0.002), grving better EFS (UK=0.65; p=0.00005) and US (OR=0.71; p=0.02) |
| FRALLE 93 LR^{21} | TTT 	imes 16 | $IV \times 6$ | Control | |
| FRALLE 93 IR^{21} | TTT 	imes 18 | $IV \times 4$ | Control | |
| SJCRH Total XIIIB ²² | IV mp + TIT \times 13 or 15 + IV \times 10 | $IV \times I$ | Control | |
| Cb: Addition of IV m | iethotrexate to long-term IT therapy (r | n=2014) | | |
| CCG-139 ²³ | $TT \times 15$ (f) or 20 (m) | IV \times 24 (f) or 33 (m) | Control | Adding IV MTX to long-term IT probably reduced CNS relapse (OR=0.78; |
| DFCI 87001 ²⁴ | $IT \times 11$ (HR: + CRT) | $\mathrm{IV} 	imes 1$ | Control | p=0.00), but did not improve EFS of OS. |
| UKALLXI LWCC ²⁵ | $\mathrm{IT} 	imes 16$ | $IV \times 3$ | Control | |
| Cc: Addition of IV me | ethotrexate to radiotherapy with TIT o | or IT therapy (n=375) | | |

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| Trial | Background CNS treatment | Arm 1 | Arm 2^* | Conclusions |
|-------------------------------|--|---|--|--|
| DFCI 81001 ²⁶ | $CSCRT + IT \times 9$ | IV 	imes 1 | Control | Adding IV MTX to CRT with short-term IT or TIT reduced CNS relapses |
| POG 9404 ²⁷ | $TIT \times 11 + CRT$ | $IV \times 4$ | Control | (OK=0.59; p=0.008) and improved EFS (OK=0.04; p=0.03), but small numbers make these results less reliable. |
| D: IV methotrexate +] | [T therapy + TIT versus extra TIT (n= | =1159) | | |
| POG8035/8036 ²⁸ | $TTT \times 6$ | $IV \times 17 + IT \times 4$ | $TIT \times 17$ | 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 ther: | apy to radiotherapy plus short-term IJ | T therapy (n=1174) | | |
| CCG-162 ³⁰ | $CRT + IT \times 6$ | $\mathrm{IT}	imes 8$ | Control | Adding extra IT therapy to CRT with short-term IT did not give benefit. |
| UKALLVII ³¹ | $CRT + IT \times 5$ | $\mathrm{IT} 	imes 8$ | Control | |
| F: Radiotherapy versu | is IV methotrexate: short-term IT, DI | T in both arms (IV MTX | in one trial) and some ad | itional IT or TIT in the IV MTX arm (n=1635) |
| CLB 7611 ³² | $IT \times 6$ | CRT | $IV \times 3$ | CRT given with short-term IT, DIT or TIT, reduced CNS relapse (OR=0.43; |
| ALL-BFM-81 ³⁴ | $\Pi 	imes 6$ | CRT | $IV \times 4$ | 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 |
| Jena ALL VII 81 ³⁵ | $\Pi 	imes 8$ | CRT | $IV \times 4$ | EFS or OS. |
| JCCLSG L-874 ³⁶ | $DIT \times 3$ | CRT | $IV\times 3+TIT\times 6$ | |
| JCCLSG I-874 ³⁶ | $IV\times 21+DIT\times 1$ | $CRT + DIT \times 2$ | $IV \times 3$ | |
| GCMTLA ³⁷ | TIT ×6 | CRT | $\mathrm{IV}\times 4+\mathrm{TIT}\times 6$ | |
| UKALLXI HWCC ²⁵ | $\mathrm{IT} 	imes 7$ or 9 | CRT | $IV \times 3 + IT \times 8 \text{ or } 9$ | |
| MRC ALL97 ³⁹ | $\mathrm{IT} \times 7$ or 9 | CRT | IV \times 3 + IT \times 8 or 9 | |
| G: Higher dose of IV n | nethotrexate (n=1071) | | | |
| POG 9405 ⁴⁰ | $TIT \times 22$ | $2.5 \text{ g/m}^2 \text{ IV} 	imes 12$ | $1 \ g/m^2 \ IV \times 12$ | No benefit from higher dose of IV MTX. |
| POG 9406 ⁴⁰ | $TIT \times 18 + 1 \ g/m^2 \ IV \ mp \times 6$ | $2.5 \text{ g/m}^2 \text{ IV} \times 6$ | $1~g/m^2~IV\times 6$ | |
| H: Higher doses of rad | liotherapy (n=905) | | | |
| UKALL V ⁴¹ | $\mathrm{IT} 	imes 5$ | 24 Gy CRT | 21 Gy CRT | No benefit from higher doses of CRT. |
| UKALLVI(i) ⁴² | $IT \times 10$ or $IT \times 8 + IV \times 3$ | 24 Gy CRT | 21 Gy CRT | |
| UKALLVI(ii) ⁴² | $IT \times 10$ or $IT \times 8 + IV \times 3$ | 24 Gy CRT | 18 Gy CRT | |
| UKALLVII ³¹ | $\mathrm{IT} 	imes 5$ | 24 Gy CRT | 18 Gy CRT | |
| GBTLI-80 ⁴³ | $TT \times 13$ | 24 Gy CRT | 18 Gy CRT | |
| TCCSG L81-10 ⁴⁴ | $DIT \times 5$ | 24 Gy CRT | 18 Gy CRT | |

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| Trial | Background CNS treatment | Arm 1 | Arm 2* | Conclusions |
|-------------------------------|---|------------------------------|--------------------------------|---|
| ALL-BFM-83 ³⁴ | $IT \times 8 + IV \times 4$ | 18 Gy CRT | 12 Gy CRT | |
| Ia: Addition of radiot | herapy to short-term IT therapy (n=475 | S) | | |
| CCG-101 ⁵⁰ | $\mathrm{IT} \times 6$ | CRT | Control | Adding CRT to 6 or 7 doses of IT reduced CNS relapses (OR=0-28; p <0-00001) |
| CCG-123 ⁵¹ | $\mathrm{IT} 	imes 7$ | CRT | Control | and improved EFS ($OR=0.68$; $p=0.005$) |
| Ib: Addition of radiot | herapy to IV methotrexate plus IT ther: | apy (n=189). | | |
| EORTC 58832 ⁵² | $IV \times 4 + IT \times 7$ | CRT | Control | Insufficient data to draw any conclusions. |
| J: Higher dose of IV n | nethotrexate versus more IT or DIT the | erapy (n=700) | | |
| FRALLE 87 ⁵³ | $DIT \times 5$ | $8~g/m^2~IV\times4$ | $3~g/m^2~IV\times4+DIT\times5$ | There was no evidence of a difference between high dose and a lower dose with |
| FRALLE 89 ²¹ | $IT \times 5$ | $8 \ g/m^2 IV \times 4$ | $3~g/m^2IV\times4+IT\times5$ | EXHALL OF DIT. |
| K: Addition of IV met | thotrexate plus IT, DIT or TIT therapy | to radiotherapy plus I1 | or TIT therapy and/or IV | methotrexate (n=511) |
| Jena ALLVII 81 ³⁵ | $CRT + IT \times 8$ | $IV\times 4+IT\times 4$ | Control | There was no evidence of a benefit from adding IV MTX with extra IT, DIT or |
| TCCSG L84-11 SR ³⁸ | $CRT + TIT \times 5 + IV \times 4 + IT \times 4$ | $IV\times 3+DIT\times 6$ | Control | 111 to a treatment which included CK1. |
| TCCSG L84-11 HR ³⁸ | $CRT + TIT \times 5 + IV \times 12 + DIT \times 12$ | $IV \times 3 + TIT \times 6$ | Control | |

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.

 $\overset{*}{}_{\rm Arm}$ 2 = Control indicates that no CNS treatment was given additional to the background.