CNS-Directed Therapy for Childhood Acute Lymphoblastic Leukemia: Childhood ALL Collaborative Group Overview of 43 Randomized Trials

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Purpose: **A collaborative meta-analysis was performed to clarify the relative effects on relapse and survival of different types of therapies directed at the CNS in childhood acute lymphoblastic leukemia.**

Materials and Methods: **Data were sought for each individual patient in all trials started in or before 1993 that included unconfounded randomized comparisons of such treatments. Log-rank survival analyses were performed for each trial, and overall results for groups of trials addressing similar questions were obtained from the totals of the observed minus expected number of events and their variances.**

Results: **Radiotherapy and long-term intrathecal therapy gave similar outcomes, with no significant difference in event-free survival despite random assignment of treatment to 2,848 patients, 1,001 of whom suffered relapse or death. Intravenous methotrexate reduced non-CNS rather than CNS relapses, and hence, the addition of intravenous methotrexate to a treatment regimen including radiotherapy or long-term intrathecal therapy improved event-free survival, with a 17% reduction in the event rate (95% confidence interval, 6% to 27%; *P* = .003). The event-free survival at 10 years in these trials was 61.9% without intravenous methotrexate and 68.1% with intravenous methotrexate. There was no significant difference in survival (14% death rate reduction; *P* = .09). There were insufficient randomly assigned patients to adequately address other questions, such as effect of different doses. No evidence was found of differences, between trials or between subgroups of different types of patients, in the relative effects of treatment.**

Conclusion: **Radiotherapy can be replaced by long-term intrathecal therapy. Intravenous methotrexate gives some additional benefit by reducing non-CNS relapses.**

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A BREAKTHROUGH in the treatment of children with acute lymphoblastic leukemia (ALL) came with the introduction of treatments that could penetrate the CNS. Trials in the late 1960s and early 1970s[1,2] established that children who received effective CNS-directed therapy had substantially superior event-free survival (EFS) and overall survival. The treatments used were initially craniospinal irradiation and then cranial irradiation, usually at a dose of 24 Gy, with short-term intrathecal therapy. However, with long-term follow-up of large numbers of children, it became apparent that there were late adverse effects, including growth and endocrine problems,[3-6] an increased risk of developing secondary tumors,[3,7-11] and possible neuropsychological sequelae.[3,12-17] With the development of alternative CNS-directed strategies, including variations in the radiotherapy dose and combinations of intrathecal treatment and high-dose intravenous methotrexate, the question is now whether alternatives expected to have fewer such side effects might be as effective for disease control.

Trials tend to be nonrandomly reported when differences are maximal, resulting in inflated estimates of treatment effects. Systematic meta-analyses using individual patient data, by obtaining additional follow-up information and including unpublished trials, reduce this bias and have many other advantages compared with reviews of the published literature.[18] To review the effectiveness of different CNS-directed treatment strategies, the Childhood ALL Collaborative Group agreed to perform a meta-analysis of all relevant randomized trials worldwide, using data on each individual patient rather than just tabular or published results.

Preliminary results were presented at a meeting of the Collaborative Group, at which the analyses to be done were discussed. After the completion of data checking and amendments, a draft manuscript was circulated to the group for comment before this final report was produced for publication.

MATERIALS AND METHODS

Although systematic reviews of randomized trials provide the best evidence on treatment effects, they are still not totally immune to bias. Such biases have been minimized as far as possible by comprehensive searching for trials, including unpublished trials, collection of data on each patient, careful data checking, and the conduct of standard analyses for each trial. In this way, the biases of concentrating only on the results of a select subset of a few trials are avoided.

Trials Included

Randomized trials of any aspect of ALL therapy were identified by electronic searching of MEDLINE, EMBASE, and clinical trial databases;

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searching meeting abstracts, review articles, and reference lists by hand; and corresponding with all members of the Childhood ALL Collaborative Group and other experts. The definition of CNS-directed therapy used was any of the following: cranial or craniospinal irradiation, intrathecal (IT) drugs, or intravenous (IV) methotrexate (MTX) or mercaptopurine (MP) at a dose of at least 500 mg/m^2, the dose at which enough of the drug will cross the blood-brain barrier to provide CNS-directed therapy. Trials were included if they involved unconfounded comparisons; that is, children were randomly assigned to treatment arms that differed only with respect to the CNS-directed therapy used. To include long enough follow-up and avoid early publication bias, only trials that began before or during 1993 are included in this review.

Data Checking

The following information was requested for each patient aged 21 years or younger at random assignment to treatment: sex, white cell count (WCC) at diagnosis; immunophenotype; treatment allocation and site of first relapse; and dates of birth, diagnosis, random assignment to treatment, first remission, relapse, and death or last contact. The data were checked by the secretariat for any internal inconsistencies; for imbalances between treatment groups with respect to initial features, randomization dates, and length of follow-up; for inconsistency with any publications; and for evidence of exclusion of randomly assigned or inclusion of nonrandomly assigned patients. Any apparent problems were clarified and rectified by correspondence with the trialists, and summary tables for each trial were sent to them for verification.

Events Analyzed

The main analyses are of EFS and survival from the date of randomization, with an event defined as any relapse or death. Secondary end points were CNS relapse (defined as any relapse with CNS involvement), non-CNS relapse, death in remission, and isolated CNS relapse. Data were obtained only for first relapse, so analyses of a particular type of relapse are censored at relapse of any other type.

Grouping of Trials and Patient Characteristics

Trials were divided into groups by the types of CNS-directed therapies they compared, with IT therapy, IV methotrexate, IV mercaptopurine, cranial irradiation, and craniospinal irradiation each counted as one type of therapy. IT therapy is usually given either for a few doses (from two to eight times) early in treatment or for longer (for between 10 and 26 doses), and these strategies were designated short IT and long IT, respectively. Results are presented for these groups of trials in descending order by the amount of information in the group, determined by the total number of events. Thus, the therapeutic questions that are most reliably answered are reported first. Variables to be used for subgroup analyses were predefined: sex, age (< 10 years and ≥ 10 years), WCC ($< 50 \times 10^9$/L and 50×10^9/L or above), and immunophenotype (B-cell lineage and T-cell lineage).

Statistics

Standard statistical methods were used.[19] The observed minus expected ($O - E$) number of events in one treatment group and its variance (V) were calculated for each trial by means of log-rank survival analyses using the exact dates of events. These quantities were then summed to give two grand totals that were used to calculate odds ratios (ORs) for annual event rates, their confidence intervals (CIs), and descriptive survival curves.

Differences in event rates are given as proportional reductions or increases and are likely to be applicable to a wide variety of patient characteristics and background treatments. The descriptive curves and the EFS and survival values at 10 years show the treatment effects in these trials in terms of absolute differences. In circumstances for which a different background event rate applies, it may be preferable to estimate the absolute difference that a particular treatment would give by using the relevant background rate together with the proportional effect from the meta-analysis. χ^2 tests of heterogeneity and trend were used to examine differences in treatment effect both between trials and between different subgroups of patients. Clearly, differences in trial protocols and patient selection will result in differences in the true effects of treatment in different trials, even when a formal test for heterogeneity is not significant. However, this does not invalidate the fixed effect or assumption-free methods used.[20]

RESULTS

When the trials were grouped by the questions they addressed, there were at least three trials and at least 400 children in each group for six questions. A total of more than 9,000 children were included in these groups. Table 1 describes the CNS-directed therapies used in these trials. Some trials were for particular risk groups of patients. Table 2 shows the numbers by age, WCC and immunophenotype, and median length of follow-up within each trial. Data checking did not reveal any problems of imbalance between treatment arms.

Most of the trials for which data were not available were older trials. The usual reasons for the unavailability of data were difficulty in extracting the information from outdated computer systems and difficulty in contacting the responsible trialist.

Figure 1 shows the ratios of annual event rates over the first 11 or more years of follow-up in trials in the main treatment comparisons. Each trial is represented by a square, with a horizontal line indicating the 99% CI. For each type of comparison the overall result is represented by a diamond, the width of which shows the 95% CI.

Comparison A: Radiotherapy Plus Intrathecal Therapy Versus Extra Intrathecal Therapy

There were eight trials in which all patients received some IT therapy and were randomly assigned to receive either cranial irradiation (XRT) or additional IT therapy. Data were available for seven of these trials, involving 2,848 children, and were only missing for one trial that involved about 350 children.[21] The overall event rate was similar with XRT (34.3%) and with extra IT therapy (36.0%), and the proportional difference in the annual event rate was a nonsignificant 4.2% reduction (95% CI, 15% reduction to 8% increase; $P = .50$) with XRT (Fig 1A). There were fewer isolated CNS relapses with XRT (XRT, 4.9%; IT therapy, 7.1%; $P = .03$). However, the nonsignificant 22% proportional reduction in the annual rate of any CNS relapse was counterbalanced by a nonsignificant 5% increase in the annual non-CNS relapse rate (Table 3). Figure 2 shows that there was little difference in terms of either overall survival (XRT, 73.5%; IT, 75.3% at 10 years) or EFS (XRT, 64.0%; IT, 62.8%).

Comparison B: Addition of IV MTX to Long-Term IT Therapy or Radiotherapy With IT Therapy

Eight trials randomized the addition of IV MTX, and data were available for all of these trials, which involved 3,189 children. All treatment arms included either irradiation and nine or more IT doses or at least 12 IT doses. The dose of IV MTX varied from 0.5 to 8 g/m^2. The annual rate of non-CNS relapses was reduced by 17% with IV MTX ($P = .02$; Table 3). The CNS relapse rate was also reduced by 19%, but this was not significant ($P = .08$), and neither was the reduction in isolated CNS relapse ($P = .1$). This resulted in a significant reduction in the annual

Table 1. Trials Analyzed

Trial Name	Year Started	Reference	CNS-Directed Therapy
A. Radiotherapy plus IT therapy versus extra IT therapy			
SWOG 7623/AlinC12	1976	21	Rand 24 Gy XRT + IT MTX × 5 *v* TIT × 22
CCG-161	1978	22	IT MTX × 6 Rand 18 Gy XRT *v* IT MTX × 8
LAL 7/78	1978	23	Rand 24 Gy XRT + IT MTX × 6 *v* DIT × 10
CCG-105	1983	24	IT MTX × 6 Rand 18 Gy XRT *v* IT MTX × 8 (F) or 14 (M)
INEN-P83	1983		IT MTX × 5 Rand 18 Gy XRT *v* IT MTX × 12
INS 84	1984	25	TIT × 6 (SR) or nil (HR) Rand 18 Gy XRT *v* TIT × 12
INEN-P85	1985		Rand 18 Gy XRT + IT MTX × 5 *v* TIT × 17
CCG-1882	1989	26	IT MTX × 14 (F) or 18 (M) + IT Ac × 1 Rand 18 Gy XRT *v* IT MTX × 7
B. Addition of IV methotrexate to long-term IT therapy or radiotherapy with IT therapy			
CCG-163d	1978	27	18 Gy XRT + IT MTX × 14 Rand ± 0.69 g/m^2 IV MTX × 8
DFCI 81001	1981	28	18 or 28 Gy CSxrt + IT Ac × 1 + IT MTX × 8 Rand ± 4 g/m^2 IV MTX × 1
CCG-139	1984	29	IT MTX × 15 (F) or 20 (M) Rand ± 0.5 g/m^2 IV MTX × 24 (F) or 33 (B)
DFCI 87001	1987	30	IT Ac × 2 + IT MTX × 10 (HR: + 18 Gy XRT) Rand ± 4 g/m^2 IV MTX × 1
UKALL XI LWCC	1990	31	IT MTX × 16 Rand ± 6–8 g/m^2 IV MTX × 3
SJCRH Total XIIIA	1991	32	TIT × 13 or 17 + 2 g/m^2 IV MTX × 9 or 10 Rand ± 1 g/m^2 IV MTX × 1
FRALLE 93 LR	1993	33	TITC × 16 Rand ± 1.5 g/m^2 IV MTX × 6
FRALLE 93 IR	1993	33	TITC × 18 Rand ± 8 g/m^2 IV MTX × 4
C. Radiotherapy plus short-term IT therapy versus IV methotrexate plus short-term TIT therapy			
CLB 7611	1976	34	IT MTX × 6 Rand 24 Gy XRT *v* 0.5 g/m^2 IV MTX × 3
ALL-BFM-81	1981	35	IT MTX × 6 Rand 12–18 Gy XRT *v* 0.5 g/m^2 IV MTX × 4
ALL VII 81	1981	36	IT MTX × 2–8 Rand 18 Gy XRT *v* 0.5 g/m^2 IV MTX × 4
D. Higher doses of radiotherapy			
UKALL V	1976	37	IT MTX × 5 Rand 24 Gy *v* 21 Gy XRT
UKALL VI(i)	1978	38	IT MTX × 8 IT Ac × 2 + 0.5 g/m^2 IV MTX × 3 Rand 24 Gy *v* 21 Gy XRT
UKALL VI(ii)	1978	38	IT MTX × 8 + IT Ac × 2 + 0.5 g/m^2 IV MTX × 3 Rand 24 Gy *v* 18 Gy XRT
UKALL VII	1979	39	IT MTX × 5 Rand 24 Gy *v* 18 Gy XRT
GBTLI-80	1980	40	IT MTX × 13 Rand 24 Gy *v* 18 Gy XRT
TCLSG L81-10	1981	41	DIT × 5 Rand 24 Gy *v* 18 Gy XRT
ALL-BFM-83	1983	35	IT MTX × 8 + 0.5 g/m^2 IV MTX × 4 Rand 18 Gy *v* 12 Gy XRT
E. Radiotherapy plus short-term IT therapy versus IV methotrexate plus long-term IT therapy			
JCCLSG L-874	1987	42	DITB × 3 Rand 18 Gy XRT *v* 2 g/m^2 IV MTX × 3 + DITB × 10
GCMTLA	1988	43	TITB × 6 Rand 12–18 Gy XRT *v* 0.5 g/m^2 IV MTX × 4 + TITB × 6
UKALL XI HWCC	1990	31	IT MTX × 7 Rand 24 Gy XRT *v* 6–8 g/m^2 IV MTX × 3 + IT MTX × 9
F. Addition of IV methotrexate plus IT therapy to radiotherapy plus IT therapy and/or IV methotrexate			
ALL VII 81	1981	44	12 or 18 Gy XRT + IT MTX × 8 Rand ± 0.5 g/m^2 IV MTX × 4 + IT MTX × 4
TCCSG L84-11 SR	1984	41	18 Gy XRT + TIT × 5 + 0.5 g/m^2 IV MTX × 4 IT MTX × 4 Rand ± 0.5 g/m^2 IV MTX × 3 + DITB × 6
TCCSG L84-11 HR	1984	41	24 Gy XRT + TIT × 5 + 0.5 g/m^2 IV MTX × 12 + DITB × 12 Rand ± 0.5 g/m^2 IV MTX × 3 + TIT × 6
G. Other comparisons, with data			
St Jude VI	1968	1	± 1 g/m^2 IV MTX × 3 Rand ± 15–24 CSxrt
St Jude VII	1970	45	Rand 15–24 Gy CSxrt *v* 15–24 Gy XRT + IT MTX × 5
CCG-101-a	1972	2	IT MTX × 6 Rand ± 24 Gy XRT
CCG-101-b	1972	2	Rand 24 Gy CSxrt (+ 12 Gy extended field) *v* IT MTX × 6
CCG-143	1974	46	Rand 18 Gy CSxrt *v* 18 Gy XRT + IT MTX × 6
CCG-162	1978	47	18 Gy XRT + IT MTX × 6 Rand ± IT MTX × 8
UKALL VII	1979	39	18 or 24 Gy XRT + IT MTX × 5 Rand ± IT MTX × 8
EORTC 58832	1983	48	2.5 g/m^2 IV MTX × 4 + IT MTX × 7 Rand ± 16–20 Gy XRT
ALL-REZ-BFM-85	1985	49	IT MTX × 9 Rand 12 g/m^2 IV MTX × 9 *v* 1 g/m^2 IV MTX × 9
FRALLE 87	1987	50	DITC × 5 Rand 8 g/m^2 IV MTX × 4 *v* 3 g/m^2 IV MTX × 4 + DITC × 5
JCCLSG I-874	1987	42	[2.0 g/m^2 × 1 + 4.5 g/m^2 × 20] IV MTX + DITB × 1 Rand 18 Gy XRT + DITB × 2 *v* 4.5 g/m^2 IV MTX × 3
EORTC 58881	1989	48	5 g/m^2 IV MTX × 4 + IT MTX × 8 Rand ± 1 g/m^2 IV MP × 18
FRALLE 89	1989	33	IT MTX × 5 Rand 8 g/m^2 IV MTX × 4 *v* 3 g/m^2 IV MTX × 4 + IT MTX × 5
ALL-REZ-BFM-90	1990	51	TITC × 9 Rand 5 g/m^2 IV MTX × 6 *v* 1 g/m^2 IV MTX × 6
Other comparisons, without data			
ALGB 6801	1968	52	Rand ± IT MTX × 15
POG CNS 2	1970	53	IT MTX × 20 Rand ± 24 Gy XRT
GATLH70a	1970	54	Rand ± XRT + ITMTX × 5
CLB 7111	1971	55	IT MTX × 6 Rand ± 24 Gy XRT
CALGB-7113	1971	56	24 Gy + IT MTX × 12 Rand ± IT MTX × 3
NCI 72-1	1971	57	24 Gy XRT Rand IT Ac × 38 *v* IT MTX × 35
SWOG 690/691/AlinC9	1971	58	TIT × 15 Rand ± 18–24 Gy XRT
DFCI-SFCC	1972	59	IT MTX × 9 Rand ± 24 Gy XRT
UKALL II	1972	60	24 Gy XRT Rand 24 Gy Sxrt *v* 10 Gy Sxrt + IT MTX × 4
CLB 7411	1974	61	IT MTX × 6 Rand ± 24 Gy XRT
POG 7712	1977	62	TIT × 6 + 24 Gy XRT Rand 14 Gy Sxrt *v* TIT × 13
NCI 77-02	1980	63	Rand 18–24 Gy XRT + IT MTX × 5 *v* 33.6 g/m^2 IV MTX × 10
POG8035/8036/AlinC13	1981	64	TIT × 6 Rand 1 g/m^2 IV MTX × 17 + IT MTX × 4 *v* TIT × 17
NCI-84-C-153A	1984		Rand 33.6 Gy/m^2 IV MTX × 10 + IT MTX × 8
JALSG ALL-87	1987	65	Rand ± IT ? × 1
DFCI ALL91-001	1991	66	4 g/m^2 IV MTX × 1 + IT Ac × 9 + IT MTX × 9 Rand ± 1 g/m^2 IV MP × 32
POG9005/AlinC15-b	1991	67	TIT × 16 Rand 1 g/m^2 IV MP × 12 *v* 1 g/m^2 IV MTX × 12
POG9005/AlinC15-c	1991	68	1 g/m^2 IV MTX × 12 + TIT × 16 Rand ± 1 g/m^2 IV MP × 12
POG9005/AlinC15-a	1991	69	TIT × 15 or 16 + 1 g/m^2 IV MP × 12 Rand oral MTX *v* 1 g/m^2 IV MTX × 12

Abbreviations: MTX, methotrexate; Ac, cytosine arabinoside; Hc, hydrocortisone; Dx, dexamethasone; P, prednisolone; MP, methylprednisolone; XRT, cranial irradiation; CSxrt, craniospinal irradiation; Sxrt, spinal irradiation; IT, intrathecal; DIT, IT MTX + IT Ac; DITB, IT MTX + IT Hc; DITC, IT MTX + IT P; TIT, IT MTX + IT Ac + IT Hc; TITB, IT MTX + IT Ac + IT Dx; TITC, IT MTX + IT Ac + IT P; SR, standard risk; HR, high risk; R, randomized.

Table 2. Patient Characteristics by Trial

	No. of Patients	Age, years			WCC			Immuno-phenotype		Median follow-up (years)
		0–9	≥ 10	%*	< 50	≥ 50	%†	C/pre-B	T	
A. Radiotherapy plus IT therapy versus extra IT therapy										
CCG-161	530	530	0	0	530	0	0	403	26	7
LAL 7/78	87	82	5	6	70	17	20	—	—	11
CCG-105	1,389	1,045	344	25	1,389	0	0	557	29	11
INEN-P83	59	45	14	24	55	4	7	—	—	8
INS 84	74	64	10	14	74	0	0	69	1	12
INEN-P85	73	62	11	15	65	8	11	—	—	5
CCG-1882	636	251	385	61	335	300	47	394	47	6
B. Addition of IV methotrexate to long-term IT therapy or radiotherapy with IT therapy										
CG-163d	321	228	93	29	0	321	100	227	52	8
DFCI 81001	77	61	16	21	58	19	25	—	—	15
CCG-139	148	112	36	24	148	0	0	78	2	11
DFCI 87001	353	285	68	19	281	72	20	319	34	8
UKALL XI LWCC	1,513	1,313	200	13	1,513	0	0	1,300	54	6
SJCRH Total XIII	162	119	43	27	0	162	100	140	22	6
FRALLE 93 LR	134	134	0	0	133	0	0	133	0	3
FRALLE 93 IR	481	432	49	10	449	32	5	479	0	3
C. Radiotherapy plus short-term IT therapy versus IV methotrexate plus short-term IT therapy										
CLB 7611	525	404	121	23	452	73	14	5	18	11
ALL-BFM-81	279	215	64	23	273	6	2	76	10	12
ALL VII 81	154	132	22	14	148	6	4	31	9	13
D. Higher doses of radiotherapy										
UKALL V	368	321	47	13	368	0	0	—	—	20
UKALL VI(i)	87	45	42	48	55	32	2	—	—	19
UKALL VI(ii)	43	17	25	60	26	17	40	—	—	18
UKALL VII	82	74	8	10	82	0	0	—	—	18
TCLSG L81-10	86	84	2	2	86	0	0	—	—	15
ALL-BFM-83	143	119	24	17	132	11	8	125	10	12
E. Radiotherapy plus short-term IT therapy versus IV methotrexate plus long-term IT therapy										
JCCLSG L-874	87	85	0	0	87	0	0	58	1	9
GCMTLA	112	94	18	16	71	41	37	—	—	8
UKALL XI HWCC	313	258	55	18	0	313	100	198	94	6
F. Addition of IV methotrexate plus IT therapy to radiotherapy plus IT therapy and/or IV methotrexate										
ALL VII 81	88	79	9	10	87	1	1	29	2	11
TCCSG L84-11 SR	187	186	0	0	187	0	0	—	—	11
TCCSG L84-11 HR	236	164	72	31	207	29	12	—	—	11

Abbreviations: WCC, white cell count; C/pre-B, B-cell lineage; T, T-cell lineage; ITT, intrathecal; IV, intravenous.

*Percentage ages ≥ 10 years.

†Percentage with WCC ≥ 50.

overall event rate of 17% (95% CI, 6% to 27%; $P = .003$) (Fig 1B), giving an improvement in EFS at 10 years of 6.2% (68.1% with IV MTX and 61.9% without IV MTX; Fig 3). There was a nonsignificant difference in survival ($P = .09$), with 10-year survival at 80.1% with IV MTX and 76.8% without IV MTX (Fig 3).

Comparison C: Radiotherapy Plus Short-Term IT Therapy Versus IV MTX Plus Short-Term IT Therapy

Three trials (all available) randomly assigned children to XRT or IV MTX. All patients received some IT therapy. Analyses of the data on 958 children showed no significant difference in EFS, with a proportional reduction of 6.5% (95% CI, 23% reduction to 13% increase) with XRT (Fig 1C). XRT reduced the CNS relapse rate by 62% ($P < .00001$; Table 3), and there was a 37%, nonsignificant reduction in deaths in first remission with XRT. In contrast, there was 67% increase in non-CNS relapse rate with XRT ($P = .00005$). Thus, there was little difference in either survival (XRT, 65.0%; IV MTX, 64.2% at 10 years) or EFS (XRT, 53.0%; IV MTX, 50.6%).

Comparison D: Higher Doses of Radiotherapy

Seven trials compared different doses of radiotherapy. All used short-term IT therapy in all treatment arms. Most trials compared 24 Gy with either 18 or 21 Gy, but one (ALL-Berlin-Frankfurt-Münster studies [BFM]-83[35]) compared 18 Gy with 12 Gy. The results of this trial were similar to the overall results, and excluding it makes little difference in the effect estimates. Data were available for all but one of the seven trials, and 809 children were included in the analyses. The missing trial randomized fewer than 200 children.[40] Figure 1D displays the EFS results from each trial. There was no significant difference between doses, with a proportional increase in the annual event rate of 1.3% with higher doses; 95% CI ranged from a decrease

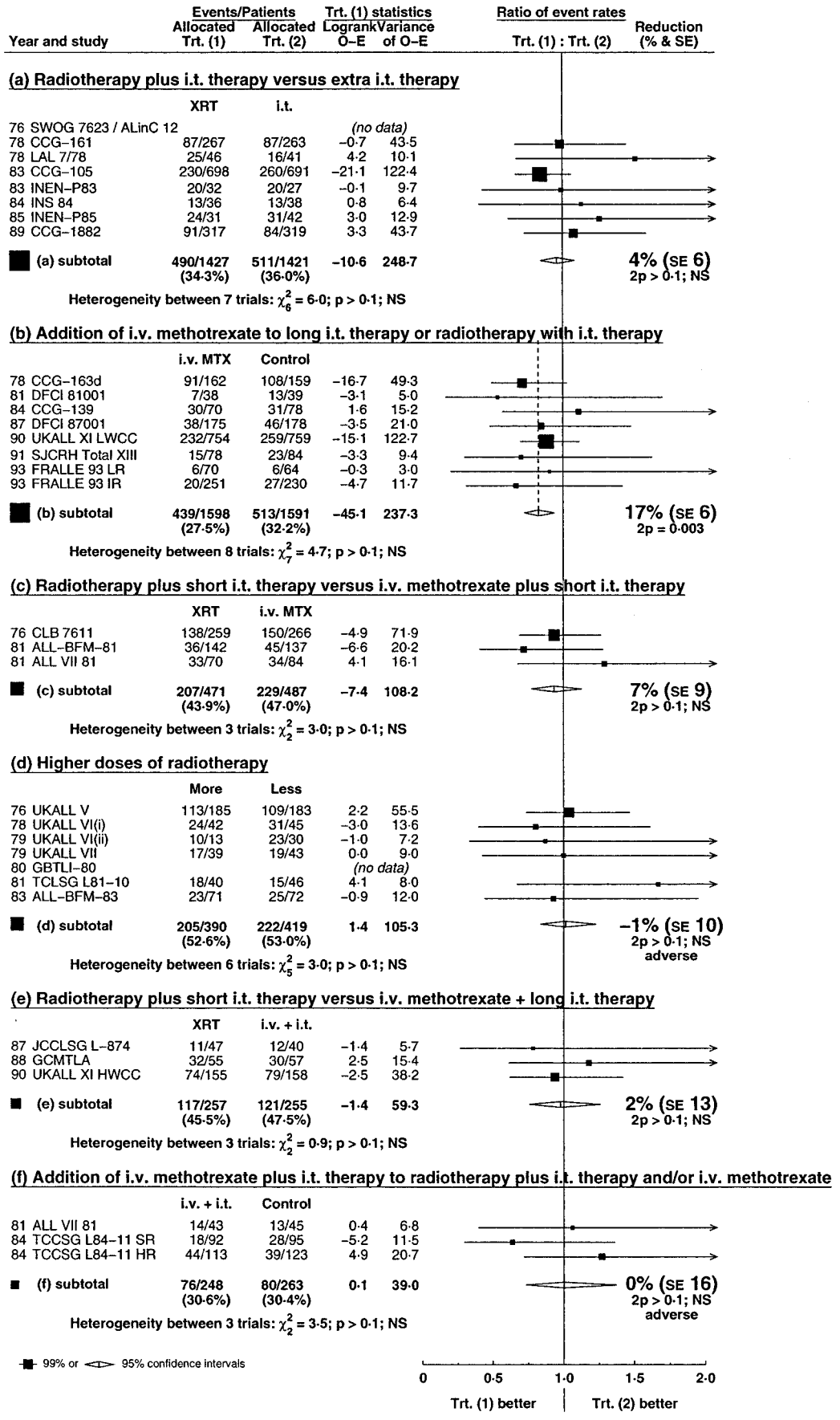


Fig 1. Effects on event-free survival for main comparisons. Ratios of annual event rates with each trial result represented by a square; larger squares indicate trials that provide more information. The overall result for each type of comparison is represented by a diamond.

Table 3. Treatment Effects on Different Sites of Relapse and Deaths in First Remission

	Numbers With Event, by Randomized Treatment		Log-Rank Odds Ratio	95% CI	*P*
A. Radiotherapy plus IT therapy versus extra IT therapy					
	XRT (n = 1,427)	IT therapy (n = 1,421)			
Any CNS relapse	90	117	0.78	0.59 to 1.03	.08
Non-CNS relapse	351	333	1.05	0.90 to 1.22	.52
Death in first remission	41	50	0.81	0.54 to 1.22	.31
Any event	490	511	0.96	0.85 to 1.08	.50
B. Addition of IV methotrexate to long-term IT therapy or radiotherapy with IT therapy					
	IV MTX (n = 1,598)	Control (n = 1,591)			
Any CNS relapse	118	145	0.81	0.63 to 1.03	.08
Non-CNS relapse	287	328	0.83	0.71 to 0.97	.02
Death in first remission	24	25	0.91	0.52 to 1.60	.76
Any event	439	513	0.83	0.73 to 0.94	.003
C. Radiotherapy plus short-term IT therapy versus IV methotrexate plus short-term IT therapy					
	XRT (n = 471)	IV MTX (n = 487)			
Any CNS relapse	37	109	0.38	0.28 to 0.53	< .00001
Non-CNS relapse	155	96	1.67	1.30 to 2.14	.00005
Death in first remission	14	23	0.63	0.33 to 1.20	.16
Any event	207	229	0.93	0.77 to 1.13	.48
D. Higher doses of radiotherapy					
	More (n = 390)	Less (n = 419)			
Any CNS relapse	30	27	1.22	0.72 to 2.06	.45
Non-CNS relapse	140	168	0.89	0.71 to 1.12	.32
Death in first remission	31	22	1.68	0.97 to 2.90	.06
Any event	205	222	1.01	0.84 to 1.23	.89
E. Radiotherapy plus short-term IT therapy versus IV methotrexate plus long-term IT therapy					
	XRT (n = 257)	IV MTX + IT (n = 255)			
Any CNS relapse	29	45	0.65	0.41 to 1.02	.06
Non-CNS relapse	79	64	1.26	0.91 to 1.75	.17
Death in first remission	7	10	0.71	0.27 to 1.83	.48
Any event	117	121	0.98	0.76 to 1.26	.86
F. Addition of IV methotrexate plus IT therapy to radiotherapy plus IT therapy and/or IV methotrexate					
	Addition (n = 248)	Control (n = 263)			
Any CNS relapse	7	13	0.59	0.24 to 1.42	.23
Non-CNS relapse	48	55	0.92	0.62 to 1.35	.67
Death in first remission	21	11	1.95	0.97 to 3.90	.06
Any event	76	80	1.00	0.73 to 1.37	.99

NOTE. Total events are not always the sum of the numbers above because of a small number of nonremitters. These are excluded from analyses of CNS relapse, non-CNS relapse, and death in first remission, but counted as having an event on day 1 in analyses of any event.

Abbreviations: CI, confidence interval; XRT, cranial irradiation; IT, intrathecal; IV, intravenous; MTX, methotrexate.

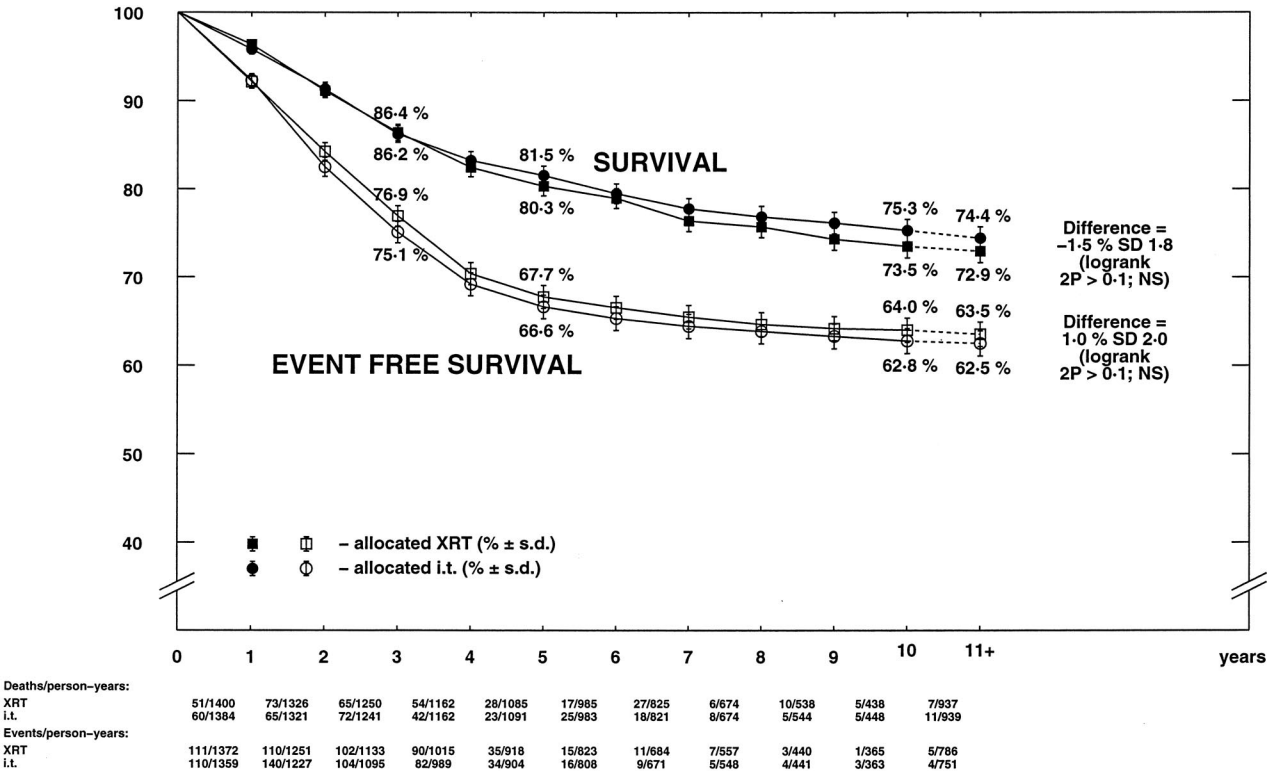
of 16% to an increase of 23%. There were also no significant differences in rates of CNS relapse (combined or isolated), non-CNS relapse, or death in remission (Table 3). Survival at 10 years was nonsignificantly greater with lower doses (59.1%) than with higher doses (55.9%), and the difference in 10-year EFS was less than 1%.

Comparison E: Radiotherapy Plus Short-Term IT Therapy Versus IV MTX Plus Long-Term IT Therapy

Three trials, involving 512 patients, compared radiotherapy versus IV MTX plus extra IT therapy. There was no significant difference in EFS (proportional reduction, 2.3%; 95% CI, 14% reduction to 26% increase; Fig 1E). At 10 years, both survival (XRT, 66.7%; IV MTX + IT, 64.7%) and EFS (XRT, 51.2%; IV MTX + IT, 49.6%) were similar with both treatments. There was no significant difference in CNS relapse between treatments, in non-CNS relapse, or in deaths in remission (Table 3). The effects were in the same direction as (but somewhat smaller than) those for the comparison of XRT with IV MTX, with a nonsignificant reduction of 35% in the CNS relapse rate and nonsignificant increase of 26% in the non-CNS relapse rate.

Comparison F: Addition of IV MTX Plus IT Therapy to Radiotherapy Plus IT Therapy and/or IV MTX

Three trials addressed the addition of IV MTX and IT therapy to other CNS therapies, including XRT. These trials randomly assigned treatment to a total of 511 children. All trials used XRT in both arms. There was no difference in EFS, with zero reduction (95% CI, 27% reduction to 37% increase; $P = .99$) in the annual event rate with the additional therapy (Fig 1F). There was no significant difference in CNS relapse between treatments, in non-CNS relapse, in deaths in first remission, or in overall survival (Table 3).



Deaths/person–years:											
XRT	51/1400	73/1326	65/1250	54/1162	28/1085	17/985	27/825	6/674	10/538	5/438	7/937
i.t.	60/1384	65/1321	72/1241	42/1162	23/1091	25/983	18/821	8/674	5/544	5/448	11/939
Events/person–years:											
XRT	111/1372	110/1251	102/1133	90/1015	35/918	15/823	11/684	7/557	3/440	1/365	5/786
i.t.	110/1359	140/1227	104/1095	82/989	34/904	16/808	9/671	5/548	4/441	3/363	4/751

Fig 2. Comparison A: Radiotherapy plus intrathecal (IT) therapy versus extra IT therapy—effects on survival and event-free survival. Descriptive curves of survival and event-free survival rates by treatment. Annual numbers of deaths, events, and person-years at risk are given beneath the graph.

Comparison G: Other Comparisons

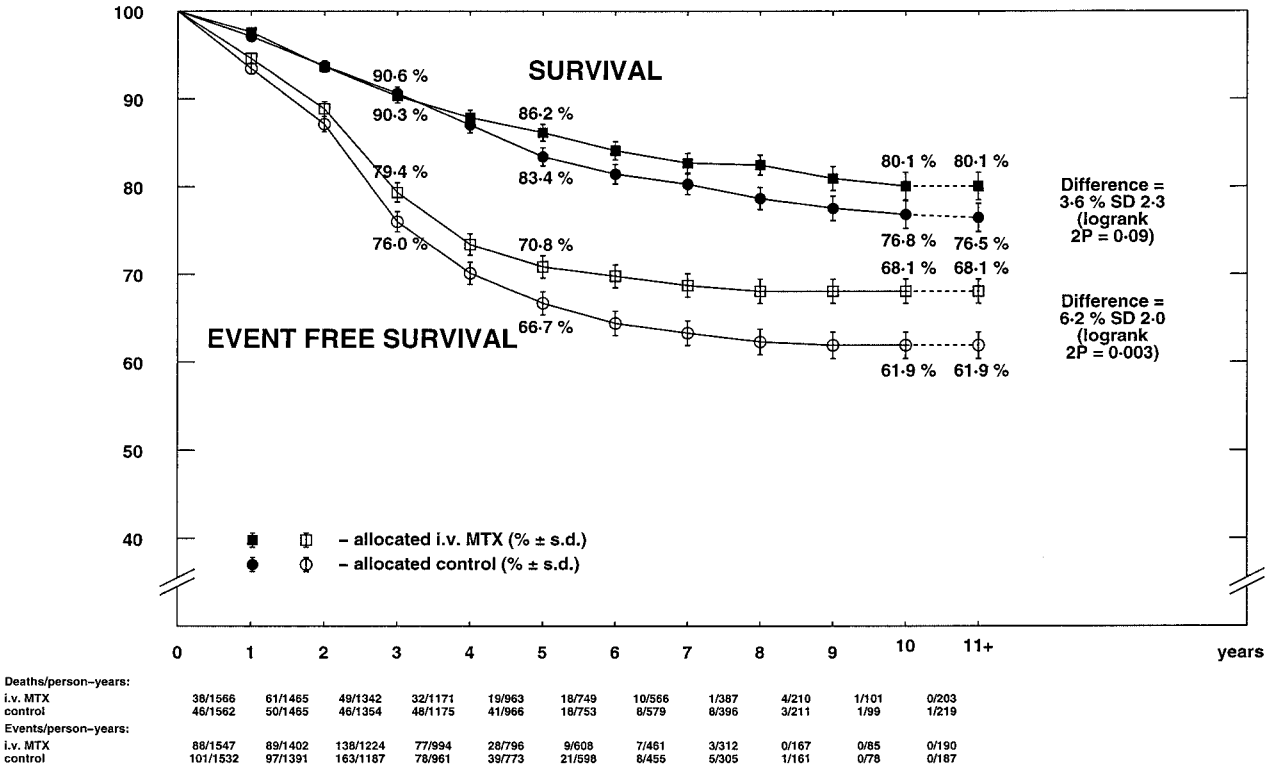
Twenty-nine randomized trials were identified that addressed treatment questions not discussed above. Data were available from 14 of these trials. Data were not requested from the Japan Adult Leukemia Study Group ALL-87 trial[65] because it was mainly an adult trial and did not address any of the main questions discussed above.

For completeness, the EFS results for each trial for which data were supplied are shown in Fig 4. The treatments are labeled as Trt1 and Trt2, referring to either the first and second randomized treatments, respectively, as specified in Table 1, or to treatment without and with the additional component, respectively, for randomized comparisons indicated by ± in Table 1, comparison G. The early St. Jude VI trial[1] showed significant benefit for craniospinal irradiation when added to a regimen without any IT treatment. The CCG-101 trial[2] showed that both XRT (comparison A) and craniospinal irradiation (comparison B) are more effective than short-term IT therapy. The CCG-162 trial,[47] and a similar comparison in United Kingdom Medical Research Council UKALL VII,[39] show that the addition of IT therapy to XRT and short-term IT therapy does not have a large effect. European Organization for Research and Treatment of Cancer trial 58881[48] suggests that repeated use of IV MP to a regimen using IV MTX and some IT therapy may be harmful. Four trials examined higher doses of IV MTX, two in relapsed patients (ALL-REZ [Rezidius]-BFM-85[49] and ALL-REZ-BFM-90[51]) and two that included more IT treatment in the lower-dose arm (French ALL Cooperative Group [FRALLE] 87[50] and FRALLE 89[33]). None of these suggested a benefit from increased dose.

Effect of Radiotherapy in Modern Protocols

Many physicians now accept that in the absence of XRT, long-term IT therapy substantially reduces CNS relapses, whereas short-term IT is insufficient.[70] This view is supported indirectly by three pieces of evidence. First, in comparison C (XRT plus short-term IT therapy *v* IV MTX plus short-term IT therapy), in which short-term IT was used, the cumulative incidence of CNS relapse rate in the no-XRT group was 28%, which is high for this intermediate-risk group of whom only 9% had high WCC, although 22% were age 10 years or older. Second, in the CCG 101 trial,[2] the isolated CNS relapse incidence was more than 35% in the no XRT arm, even though only 15% had high WCC and 16% were age 10 years or older. Third, in the trials in comparisons A (XRT plus IT therapy *v* extra IT therapy) and E (XRT plus short-term IT therapy *v* IV MTX plus long-term IT therapy), there were only 12% CNS relapses in the no-XRT arms, all of which used long-term IT, even though the patients included were relatively high risk (12% with high WCC and 27% age 10 years or older in comparison A, and 69% high WCC and 14% age 10 years or older in comparison E).

Therefore, can XRT be replaced by long-term IT therapy for the prevention of CNS relapse? Comparison C (XRT plus short-term IT therapy *v* IV MTX plus short-term IT therapy)



Deaths/person–years:											
i.v. MTX	38/1566	61/1465	49/1342	32/1171	19/963	18/749	10/566	1/387	4/210	1/101	0/203
control	46/1562	50/1465	46/1354	48/1175	41/966	18/753	8/579	8/396	3/211	1/99	1/219
Events/person–years:											
i.v. MTX	88/1547	89/1402	138/1224	77/994	28/796	9/608	7/461	3/312	0/167	0/85	0/190
control	101/1532	97/1391	163/1187	78/961	39/773	21/598	8/455	5/305	1/161	0/78	0/187

Fig 3. Comparison B: Addition of intravenous (IV) methotrexate to long-term intrathecal (IT) therapy or radiotherapy with IT therapy—effects on survival and event-free survival. Descriptive curves of survival and event-free survival rates by treatment. Annual numbers of deaths, events, and person-years at risk are given beneath the graph.

shows that the main effect of IV MTX is on non-CNS relapse. If we assume little effect of IV MTX on CNS relapse, comparisons A (XRT plus short-term IT therapy *v* extra IT therapy) and E (XRT plus short-term IT therapy *v* IV MTX plus long-term IT therapy) can be combined to determine the relative effects of XRT plus some IT therapy and long-term IT alone on CNS relapse. This shows that XRT may be a little more effective, with 8.4% cumulative CNS relapse in the XRT group compared with 11.8% in the long-term IT group, a difference of 3.4%. In fact, the number of additional cures may well be less than 3.4% because in comparison A (XRT plus short-term IT therapy *v* extra IT therapy), the 2.5% reduction in CNS relapses is counterbalanced by a 1.1% increase in non-CNS relapses, and some of the CNS relapses prevented by XRT might be curable, as there are 57 (63%) deaths among the 90 patients with CNS relapse in the XRT group, and only 54 deaths (46%) among the 117 patients in the long-term IT therapy arm. Thus, although there are more CNS relapses with long-term IT therapy, a larger proportion can be successfully re-treated.

Although using long-term IT therapy with XRT might provide additional benefit, there are concerns about its adverse effects on the brain,[71-73] and there is a lack of evidence in favor of the treatment. The CCG-162 trial[47] (which included more than 1,000 children) and UKALL VII,[39] both of which addressed the question of whether extra IT therapy should be added to XRT plus short-term IT, did not indicate additional prevention of CNS relapse and exhibited 1% more such relapses in the additional IT group.

Effect of IV MTX

High-dose IV MTX was introduced as a treatment that might be expected to prevent CNS relapse because of evidence that it could cross the blood-brain barrier. The question of whether this is the case in practice is addressed by comparison C (XRT plus short-term IT therapy *v* IV MTX plus short-term IT therapy), which clearly shows that high-dose IV MTX is not as effective as XRT in preventing CNS relapse. However, it seems that many of the patients who would have relapsed in the CNS without adequate CNS-directed treatment relapsed instead at another site. IV MTX prevents these non-CNS relapses.

Does the addition of IV MTX to a schedule with adequate CNS-directed therapy also provide benefit, not in terms of CNS protection, but against non-CNS relapse? Comparisons B (addition of IV MTX to long IT therapy or XRT with IT therapy) and E (XRT plus short-term IT therapy *v* IV MTX plus long-term IT therapy) show that, among patients receiving standard CNS-directed treatment, IV MTX reduces the non-CNS relapse rate by 4.6%, with an incidence of 28.3% in the no–IV MTX arm compared with 23.8% in the IV MTX arm. Because it has no significant effect on CNS relapse, overall EFS is better with IV MTX than without it.

Investigation of Heterogeneity

No significant heterogeneity of effect was found within any of the main comparisons, either between trials or between patient subgroups based on sex, WCC, or immunophenotype. However, only limited data were available on immunophenotype (Table 2).

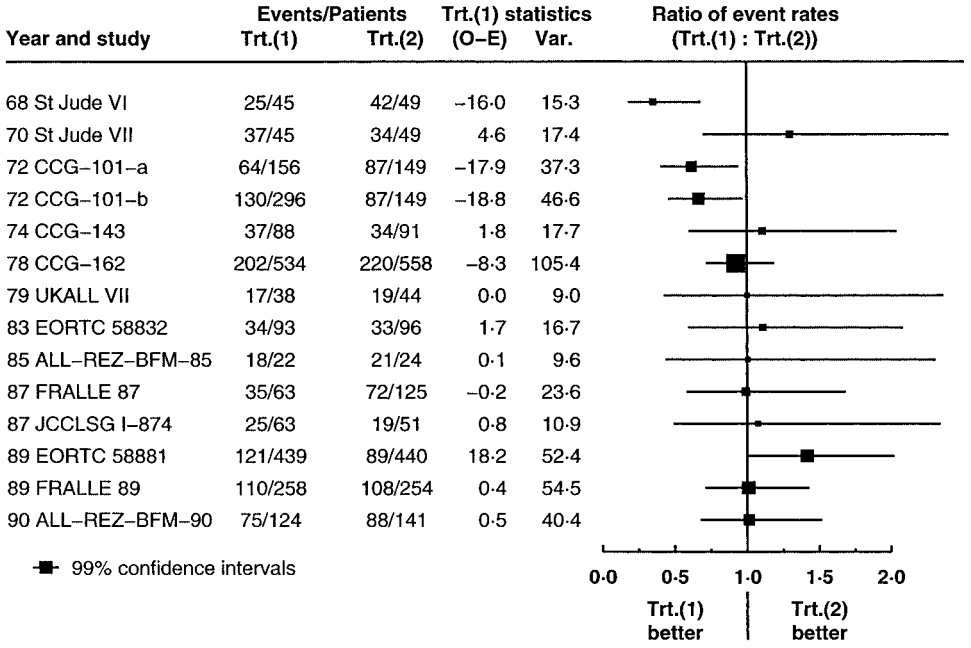


Fig 4. Effects on event-free survival in other trials. Format as Fig 1. Trt1 and Trt2 refer to either the first and second randomized treatments, respectively, as specified in Table 1G, or to treatment without and with the additional component indicated by ± in Table 1G.

The only suggestion of heterogeneity was with respect to non-CNS relapse by age in comparison C (XRT plus short-term IT therapy *v* IV MTX plus short-term IT therapy; $P_{het} = 0.01$), but given the number of tests done, it is not surprising to find one with this level of significance as a result of chance alone. In addition, combining comparisons B (addition of IV MTX to long-term IT therapy or XRT with IT therapy) and E (XRT plus short-term IT therapy *v* IV MTX plus long-term IT therapy) does not show a different effect by age group for non-CNS relapse ($P_{het} = 0.7$). Thus, for patients receiving adequate CNS-directed therapy, IV MTX does not have a different effect on non-CNS relapses in the different age groups.

DISCUSSION

Analyses of survival have been included, as it is important to determine whether differences in EFS also translate into survival benefit. Although survival is dependent on both initial treatment and on salvage treatment for those who relapse, and the latter will have been variable in these trials, it is important to know the results for overall survival. For example, if a treatment improved EFS but overall survival was worse, we would want to be aware of this so that the reasons for it could be examined.

Follow-up was generally more complete for trials with shorter median follow-up. The proportion of survivors lost to follow-up 3 or more years before the final follow-up date was less than 10% for trials with a median follow-up of less than 8 years, but varied from 0% to 40% for trials with longer median follow-up. This must be borne in mind when long-term effects are considered. The numbers at risk shown below the survival curves indicate how many patients remain in the analyses and, hence, how much confidence one can have in the right-hand ends of the curves.

The most reliable results are those based on the largest numbers of events. Thus, we can be fairly sure, based on comparisons including more than 1,000 events, that XRT reduces CNS relapses slightly more than long-term IT therapy (about 3% absolute benefit) and that there is no evidence of particular benefit in any subgroup.

From the trials included in this review, most of which used 18 or 21 Gy as the standard dose, there was no evidence that higher doses of XRT were of benefit.

One of the advantages of systematic reviews is that, with the larger numbers available, false-negatives are less likely than with each individual trial. Adding IV MTX to regimens containing either XRT and short-term IT therapy or long-term IT therapies leads to improved EFS, and this result is based on almost 1,000 events. This is an example where the meta-analysis demonstrates a definite effect ($P = .003$) that was not clear from the individual trial results; only one of the eight trials addressing this question showed statistical significance at the $P = .05$ level.

From the comparisons of XRT versus IV MTX, with some IT MTX used in both arms, it is clear that the principal effect of IV MTX is on non-CNS relapse; and other ways of intensifying treatment have been established that reduce bone marrow relapses and improve EFS.[74] The EFS in the trials of the addition of IV MTX to adequate CNS-directed therapy was 65% at 10 years, and newer protocols using more intensive systemic treatment, particularly for high-risk patients, might be expected to produce a higher long-term EFS. Because, in general, the proportional effect of a treatment remains similar over different circumstances (unless there is a definite reason to expect an interaction between treatment components), the expected absolute increase in EFS with IV MTX for patients with a baseline EFS of 70% to 80% would be 4% to 5%, rather than the 6% seen in these trials.

The IV MTX dose used varied from 0.5 to 8 g/m^2, and from one to 33 courses, with the total cumulative dose varying from 1 to 32 g/m^2. The dose was at least 5 g/m^2 in the majority of cases.

Most physicians currently do not believe that 0.5 g/m^2 gives useful CNS levels, and many question whether even 5 g/m^2 does so. There is little direct evidence on the effect of different doses, because only the French trials (FRALLE 87[50] and FRALLE 89[33]), which also used extra IT therapy in the lower dose arm, and the German relapse trials (ALL-REZ-BFM-85[49] and ALL-REZ-BFM-90[51]) compared different doses. Thus, there are insufficient data to demonstrate whether any additional benefit is accrued from higher doses. In addition, no suggestion of a trend in the effect was seen if an attempt was made to order the trials by intensity of IV MTX treatment (comparison B ordered by dose or by cumulative dose produced *P* values for trends of 0.7 and 0.3, respectively).

There have been many suggestions that treatment effects differ in subgroups, such as high versus low WCC, T- versus B-cell lineage disease, and so on. These suggestions are not substantiated by the evidence in this review, although the limited data on immunophenotype, and in particular the small numbers involving T-cell lineage disease, mean that great uncertainty remains for this subgroup.

All results need to be viewed in the context of other factors, including long-term side effects. Neuropsychological effects of the different treatments still require further evaluation to determine which treatments are damaging, how severe the long-term effects are, and which subgroups of children are most affected. Recent nonrandomized comparisons of children receiving chemotherapy regimens plus XRT with other children receiving chemotherapy alone, and with healthy controls, indicate that XRT causes learning problems.[71-73] One retrospective comparison of children from a randomized trial of XRT versus intermediate-dose IV MTX showed poorer long-term psychosocial functioning with XRT.[75] Further information will become available in due course, which may clarify lasting neuropsychological effects by age group and treatment, from the prospective studies attached to the randomized trial CCG-105 of continuing IT MTX versus XRT,[76] and the UKALL XI trial of IT MTX plus high-dose IV MTX versus XRT or continuing IT MTX alone.[77]

In conclusion, XRT can be replaced by long-term IT therapy without detriment to EFS or overall survival. Intravenous MTX at doses of at least 0.5 g/m^2 (and 5 g/m^2 cumulative dose) improves EFS by a few percent but does not have much effect on overall survival. This review only provides information on the effects of treatment on events, and clinical decisions clearly need to also take into consideration other factors such as side effects and inconvenience.

APPENDIX

The appendix is available online at www.jco.org.

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