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ORIGINAL REPORT

Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy

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ABSTRACT

Purpose
We sought to determine whether cranial radiotherapy (CRT) is necessary to prevent relapse in any subgroup of children with acute lymphoblastic leukemia (ALL).

Patients and Methods
We obtained aggregate data on relapse and survival outcomes for 16,623 patients age 1 to 18 years old with newly diagnosed ALL treated between 1996 and 2007 by 10 cooperative study groups from around the world. The proportion of patients eligible for prophylactic CRT varied from 0% to 33% by trial and was not related to the proportion eligible for allogeneic stem-cell transplantation in first complete remission. Using a random effects model, with CRT as a dichotomous covariate, we performed a single-arm meta-analysis to compare event-free survival and cumulative incidence of isolated or any CNS relapse and isolated bone marrow relapse in high-risk subgroups of patients who either did or did not receive CRT.

Results
Although there was significant heterogeneity in all outcome end points according to trial, CRT was associated with a reduced risk of relapse only in the small subgroup of patients with overt CNS disease at diagnosis, who had a significantly lower risk of isolated CNS relapse (4% with CRT *v* 17% without CRT; $P = .02$) and a trend toward lower risk of any CNS relapse (7% with CRT *v* 17% without CRT; $P = .09$). However, this group had a relatively high rate of events regardless of whether or not they received CRT (32% [95% CI, 26% to 39%] *v* 34% [95% CI, 19% to 54%]; $P = .8$).

Conclusion
CRT does not have an impact on the risk of relapse in children with ALL treated on contemporary protocols.

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INTRODUCTION

Although it has been standard practice for prevention of CNS relapse in older treatment protocols for children with acute lymphoblastic leukemia (ALL),[1] pre-emptive cranial radiotherapy (CRT) has increasingly been replaced by other treatment strategies[2-4] because of its associated high risk of late neurocognitive sequelae,[5,6] endocrinopathy,[7] and secondary cancers.[8,9] A systematic review and meta-analysis of 47 randomized trials of CNS-directed therapy conducted between the 1970s and 1990s showed that CRT can generally be replaced by intrathecal therapy.[10] This observation has been confirmed in single-group studies[11-13] and in a more recent meta-analysis on T-lineage ALL only.[14] In parallel, all major collaborative ALL study groups have decreased the percentage of patients who receive CRT. Those who use CRT now generally restrict this treatment modality to patients presumed to be at increased risk of relapse in the CNS or at other sites,[15] typically including subgroups such as those with overt CNS disease present at initial diagnosis, T-cell immunophenotype, high initial WBC count, or slow early response. However, review of current practice within an intergroup collaboration of 10 major childhood ALL treatment groups from around the world revealed large differences in the proportion of newly diagnosed patients assigned to receive CRT, ranging from 0% to 33%. This variation allowed us to perform a meta-analysis to determine

Table 1. Characteristics of the Included Trials

Group	Trial (Years of Recruitment)	No. of Patients	CRT		SCT	
			% of Patients	Indications	Percent of Patients	Indications
AIEOP	ALL 2000 (2000-2006)	1,999	18	CNS3*, t(4;11) T cell with WBC > 100×10^9/L, T cell and B cell with slow early response (prednisone poor response) or no CR at day 33 or high-risk MRD ($\geq 5 \times 10^{-4}$) at week 12	4	t(4;11); slow early response (prednisone poor response) and WBC > 100×10^9/L or T cell or pro-B or MRD $\geq 5 \times 10^{-3}$ at day 33; no CR at day 33; high risk MRD ($\geq 5 \times 10^{-4}$) at week 12
BFM	ALL 2000 (2000-2007)	3,582	18	CNS3*, t(4;11) T cell, B cell with slow early response (prednisone poor response) or no CR at day 33 or high risk MRD ($\geq 5 \times 10^{-4}$) at week 12	5	t(4;11); slow early response (prednisone poor-response) and WBC > 100×10^9/L or T cell or pro-B or M3 BM at day 15; no CR at day 33; high-risk MRD ($\geq 5 \times 10^{-4}$) at week 12
COALL	06-97 and 07-03 (1997-2003)	910	12	CNS3 for both protocols. For 06-97: T cell and B cell with WBC > 100×10^9/L. For 07-03: T cell with WBC > 50×10^9/L, B cell with WBC > 200×10^9/L and with WBC 100-200 $\times 10^9$/L and > 1×10^9/L blasts in the PB after prophase	4	For 06-97: no remission at day 29, t(4;11) high-risk patients and high (8 + 9) score for in vitro responsiveness to PVA. For 07-03: no remission at day 29, t(4;11)
COG	POG 9900 (B-ALL; 1999-2005)† and POG 9404 (T-ALL; 1996-2001)	3,182	15	T-ALL: all patients; CNS3	3	M3 BM at end induction or hypodiploid ALL (not included in these analyses)
DCOG	ALL9 (1997-2004)	859	0	Standard no CRT	3	*MLL* positive
JACLS	ALL02 (2002-2008)	1,246	10	CNS3, T cell with WBC > 100×10^9/L	5	Slow early response, induction failure, M3 BM at day 15 in high-risk patients, *MLL* positive, < 44 chromosomes
NOPHO	ALL 2000 (2002-2008)	1,082	14	CNS3, T cell with mediastinal mass, T cell and B cell with WBC 100-200 $\times 10^9$/L; for all, only if age > 5 years at diagnosis	6	WBC $\geq 200 \times 10^9$/L, slow response with no CR at end of induction (M3 bone marrow at day 29), *MLL* positive if $\geq$ 10 years, < 34 chromosomes
SJCRH	Total Therapy Study XV (2000-2007)	488	0	Standard no CRT	5	Induction failure or > 1% leukemic lymphoblasts in the bone marrow on remission date, > 0.1% leukemic lymphoblasts in the BM in week 7 of continuation treatment, re-emergence of leukemic lymphoblasts by MRD in patients previously negative for MRD
UK	ALL 2003 (2003-2011)	2,783	2	CNS3	2	t(17:19), *MLL* positive, < 44 chromosomes and M2 BM at day 28, M3 BM at day 28
DFCI	00-01 (2000-2004)	492	33	T cell and B cell with CNS3 and/or WBC > 100×10^9/L	2	Induction failure (M2 or M3 BM at end of first month of treatment)

Abbreviations: AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; ALL, acute lymphoblastic leukemia; B-ALL, B cell acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; BM, bone marrow; COALL, Cooperative Acute Lymphoblastic Leukemia Group; COG, Children's Oncology Group; CNS3, overt CNS involvement; CR, complete remission; CRT, cranial radiotherapy; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute; JACLS, Japanese Childhood Leukemia Study Group; MRD, minimal residual disease; NOPHO, Nordic Pediatric Hematology and Oncology Study Group; PB, peripheral blood; POG, Pediatric Oncology Group; PVA, prednisolone, vincristine, and asparaginase; SJCRH, St Jude Children's Research Hospital; T-ALL, T cell acute lymphoblastic leukemia; UK, United Kingdom and Ireland Group.

*Includes patients with retinal infiltrates and cerebral/meningeal involvement on imaging in addition to those with blasts in CSF. Patients with normal CSF account for 52 of the 110 BFM patients included as having CNS3.

†POG 9900 was not included in subgroup analysis because postinduction therapy details were not available.

whether there was evidence that CRT is necessary for any subgroup of patients.

PATIENTS AND METHODS

We performed a retrospective analysis of data from 10 cooperative study groups (Table 1) in Europe, North America, and Asia. From January 1996 through December 2011, the study groups had enrolled in clinical trials a total of 16,623 patients age 1 to 18 years old with newly diagnosed ALL. The enrollment period was chosen to ensure that the systemic treatment was contemporary and to allow for sufficient follow-up.

Data were obtained from the groups through a clinical data acquisition form and included the 5-year estimates and SEs of survival, overall cumulative incidence of any event (defined as the first event among death, no complete remission [CR], relapse, and development of a second malignancy, and corresponding to 100% minus event-free survival [EFS]), crude cumulative incidence of isolated bone marrow relapses, isolated CNS relapses, and combined relapses with CNS involvement. We collected data

on outcome of all patients treated on the trial, as well as the following subgroups that are known to be at high risk of CNS relapse and had significant variability in the CRT policy used by different study groups: patients with overt CNS involvement at diagnosis (CNS3), defined as five or more leukocytes per microliter and less than 10 RBCs per microliter in CSF with blasts on cytospin (except Associazione Italiana Ematologia ed Oncologia Pediatrica [AIEOP]–Berlin-Frankfurt-Münster [BFM] ALL 2000, which also included patients presenting with retinal infiltrates and cerebral/meningeal involvement on imaging); and patients with B- or T-cell ALL with presenting WBC count greater than 100×10^9/L or slow early response (defined as either persistent circulating blasts $> 1 \times 10^9$/L after 7 days of single-agent prednisolone [prednisone poor responders] or $\geq$ 25% blasts in the marrow after 7 to 14 days of induction chemotherapy). Infants younger than 1 year old and patients with Philadelphia chromosome–positive ALL were excluded, because these subgroups were treated on separate intergroup protocols in several countries. In addition, B-cell subgroups from Children's Oncology Group (COG) studies were not included in the analysis because there were insufficient details on postinduction therapy for these groups. The estimates were provided for the selected subgroups of patients, and information on the subgroups eligible for CRT was also collected. Because patients who are allocated to receive stem-cell transplantation (SCT) in first CR generally receive total-body irradiation as part of the transplantation preparative regimen, only relapses before SCT in first CR were considered; survival, overall cumulative incidence of events, and crude cumulative incidence curves were censored at the date of SCT in first CR.

All of the clinical trials from which data were used in this analysis had previously received approval from the relevant institutional review boards or ethics committees, and written informed consent had been obtained from patients or their parent(s) or guardian(s) according to local regulations.

Treatment

Systemic and CNS-directed treatment varied considerably between trials; details of risk stratification and treatment regimens within individual trials have been published elsewhere.[3,12,13,16-23] Regardless of whether a patient subgroup was eligible for CRT, the vast majority of patients received infusions of high-dose (≥ 5 g/m^2) or intermediate-dose methotrexate (1 to 5 g/m^2) with leucovorin rescue. Exceptions included COG patients with T-cell ALL (T-ALL) who participated in the Pediatric Oncology Group 9404 randomized trial of therapy with or without high-dose methotrexate and slow early responders in the United Kingdom ALL (UKALL) 2003 trial who received two courses of Capizzi-style, escalating-dose intravenous methotrexate without leucovorin rescue. The indications for and proportion of patients eligible for CRT and SCT differed by trial and are listed in Table 1. Fractionated CRT was administered at a dose of 12 to 24 Gy depending on patient subgroup. There was no relationship between the proportion of patients eligible for CRT (0% to 33%) and that eligible for first CR allogeneic SCT (2% to 6%). Thus, trials in which fewer patients were eligible for CRT did not have a higher proportion eligible for SCT.

Statistical Analysis

Our approach was a one-arm meta-analysis for aggregate data. For each subgroup of patients, as defined earlier, each participating group provided 5-year estimates and SEs of relevant outcome measures calculated with a common approach in all trials, which consisted of the Kaplan-Meier method for survival and overall cumulative incidence and the Aalen-Johansen estimator for crude cumulative incidences. All curves were censored at the date of SCT in first CR. Each group also provided the number of the various events for each subgroup of patients (Data Supplement). For all outcomes, we first performed a meta-analysis of all the trials using a generalized linear mixed model (GLMM), assuming a binomial distribution within study for the 5-year estimates of the previously mentioned functions.[24] We used a GLMM because, in some subgroups, the crude cumulative incidence was equal to 0 in one or more studies and the classic inverse-variance approach[25] would exclude these studies for the inability to calculate the variance.[24,26] In contrast, GLMMs allow one to easily include in a meta-analysis studies with no events without the need for arbitrary corrections and were shown, by simulation, to have a good performance with low incidences in a competing risk setting.[24] We used a random effects model, because the different groups used different first-line treatment protocols, suggesting that a common fixed parameter for the real effect cannot be assumed.

For all subgroups, we then applied the same model with a dichotomous covariate to compare each outcome on the basis of whether or not pre-emptive CRT was given in the protocol. We calculated 95% CIs for the summary estimates and 99% CIs for the primary studies to account for multiple comparisons. The latter were calculated using SEs provided by each group; to maintain the bounds of the CIs between 0 and 1, we used the cloglog transformation for the 5-year cumulative and crude cumulative incidence estimates.[27] All analyses were performed using R (version 3.0; R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and the R package metafor.[28]

Table 2. Patients by Protocol in Each Analyzed Subgroup

Group	No. of Patients in Subgroup (%)					Total No. of Protocol Patients
	CNS3	T-Cell, WBC > 100×10^9/L	B-Cell, WBC > 100×10^9/L	T Cell, Slow Early Response	B Cell, Slow Early Response	
AIEOP	44 (2.2)	100 (5.0)	100 (5.0)	79 (4.0)	128 (6.4)	1,999
BFM	110 (3.1)	184 (5.1)	179 (5.0)	179 (5.0)	172 (4.8)	3,582
COALL	18 (2.0)	47 (5.2)	48 (5.3)	52 (5.7)	226 (24.8)	910
COG	67 (2.1)	144 (4.5)	NA*	55 (1.7)	NA*	3,182
DCOG	21 (2.4)	47 (5.5)	57 (6.6)	NA	NA	859
JACLS	41 (3.3)	39 (3.1)	64 (5.1)	40 (3.2)	80 (6.4)	1,246
NOPHO	31 (2.9)	64 (5.9)	61 (5.6)	13 (1.2)	51 (4.7)	1,082
SJCRH	8 (1.6)	34 (7.0)	26 (5.3)	21 (4.3)	68 (13.9)	488
UK	49 (1.8)	167 (6.0)	168 (6.0)	80 (2.9)	227 (8.2)	2,783
DFCI	17 (3.5)	18 (3.7)	32 (6.5)	NA	NA	492

Abbreviations: AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; COALL, Cooperative Acute Lymphoblastic Leukemia Group; COG, Children's Oncology Group; CNS3, overt CNS involvement; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute; JACLS, Japanese Childhood Leukemia Study Group; NA, not available; NOPHO, Nordic Pediatric Hematology and Oncology Study Group; POG, Pediatric Oncology Group; SJCRH, St Jude Children's Research Hospital; UK, United Kingdom and Ireland Group.
*POG 9900 was not included in subgroup analysis because postinduction therapy details were not available.

RESULTS

Data were available for 16,623 patients treated on 10 cooperative group trials. The numbers of patients included from within individual trials by subgroups analyzed are listed in Table 2. Depending on the definition of early response, there was a difference in proportion of patients categorized as slow responders by trial. Two trials (Dana-Farber Cancer Institute [DFCI] 00-01 and Dutch Children's Oncology Group 9 trials) did not stratify patients by early response. The proportion of other subgroups was similar across trials.

As shown in Figure 1, there was significant heterogeneity among trials in the cumulative incidence of any event and overall survival. However, when aggregate outcomes were compared among trials in which the particular subgroup received or did not receive CRT (Fig 2 and Table 3), there was no evidence of an effect of CRT on any end point in any subgroup of patients except CNS relapses in patients with CNS3 (Fig 2C). In this subgroup, the cumulative risk of any event (Fig 2A) was relatively high but not related to whether CRT was administered (summary estimates in bold in Fig 2: no CRT, 34.4% [95% CI, 19.0% to 53.8%]; with CRT, 32.2% [95% CI, 26.2% to 38.8%]; $P = .8$). However, the rates of isolated CNS relapse (Fig 2C) and any CNS relapse (Fig 2D) were higher for patients with CNS3 in trials without CRT versus with CRT (16.7% [95% CI, 6.4% to 36.9%] *v* 4.3% [95% CI, 2.6% to 7.2%]; $P = .02$; and 16.7% [95% CI, 6.4% to 36.9%] *v* 6.8% [95% CI, 4.5% to 10.1%]; $P = .09$, respectively), whereas those for BM relapse (Fig 2B) were slightly lower (8.3% [95% CI, 2.8% to 22.0%] *v* 10.5% [95% CI, 7.9% to 13.9%], respectively; $P = .67$). The 5-year mortality rates were not significantly different between patients with CNS3 treated with or without CRT (22.4% [95% CI, 17.2% to 27.7%] *v* 20.6% [95% CI, 4.3% to 36.9%], respectively; $P = .83$).

Although the overall survival for patients with T-ALL with slow early response was significantly higher in the no CRT studies

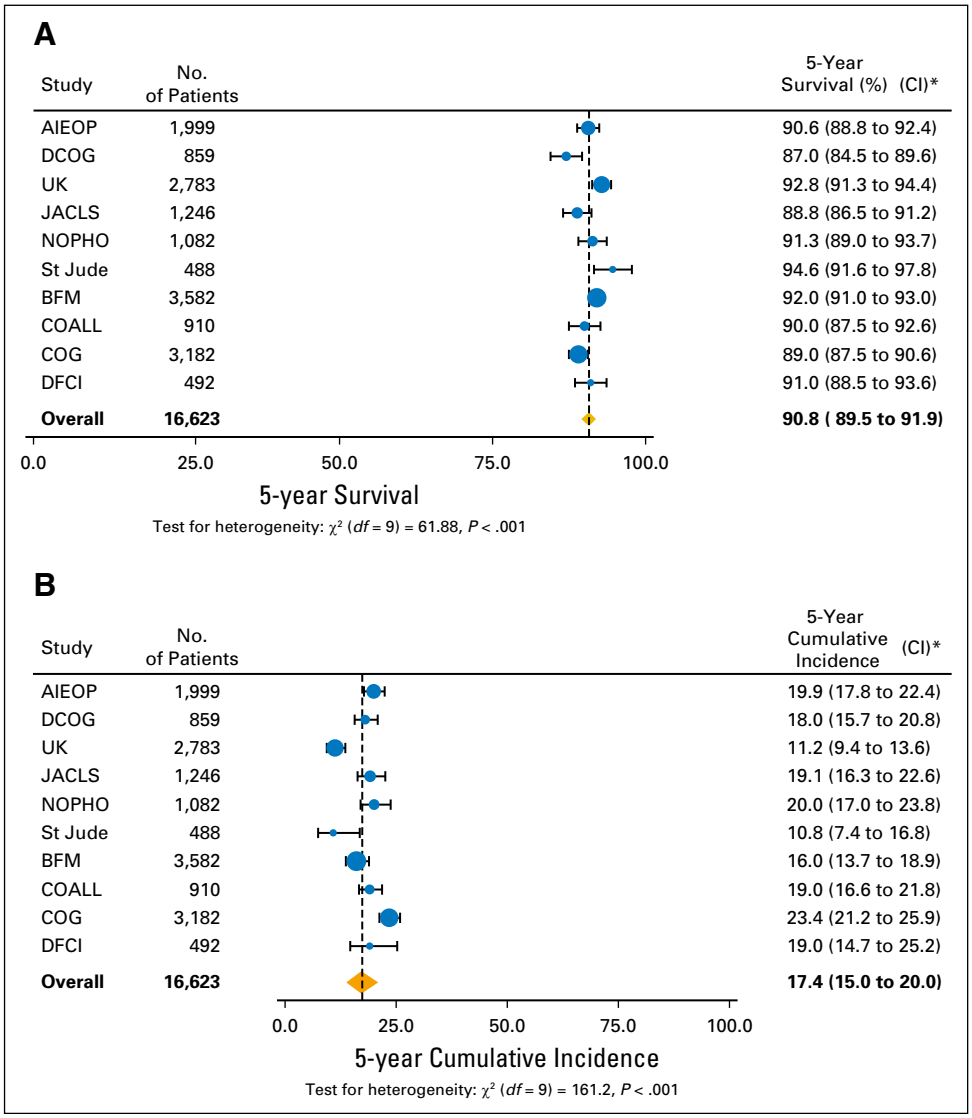

Fig 1. Five-year (A) overall survival and (B) cumulative incidence of any event for all patients included in the protocols. Forest plots present the raw cumulative 5-year estimates for each protocol, with the 99% CIs. The meta-analysis summary estimate, model based, is presented in the form of a diamond (its width represents the 95% CI). *CIs are 99% CIs for primary study effects and 95% CIs for summary effects. AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; COALL, Cooperative Acute Lymphoblastic Leukemia Group; COG, Children's Oncology Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute; JACLS, Japanese Childhood Leukemia Study Group; NOPHO, Nordic Pediatric Hematology and Oncology Study Group; UK, United Kingdom and Ireland Group.

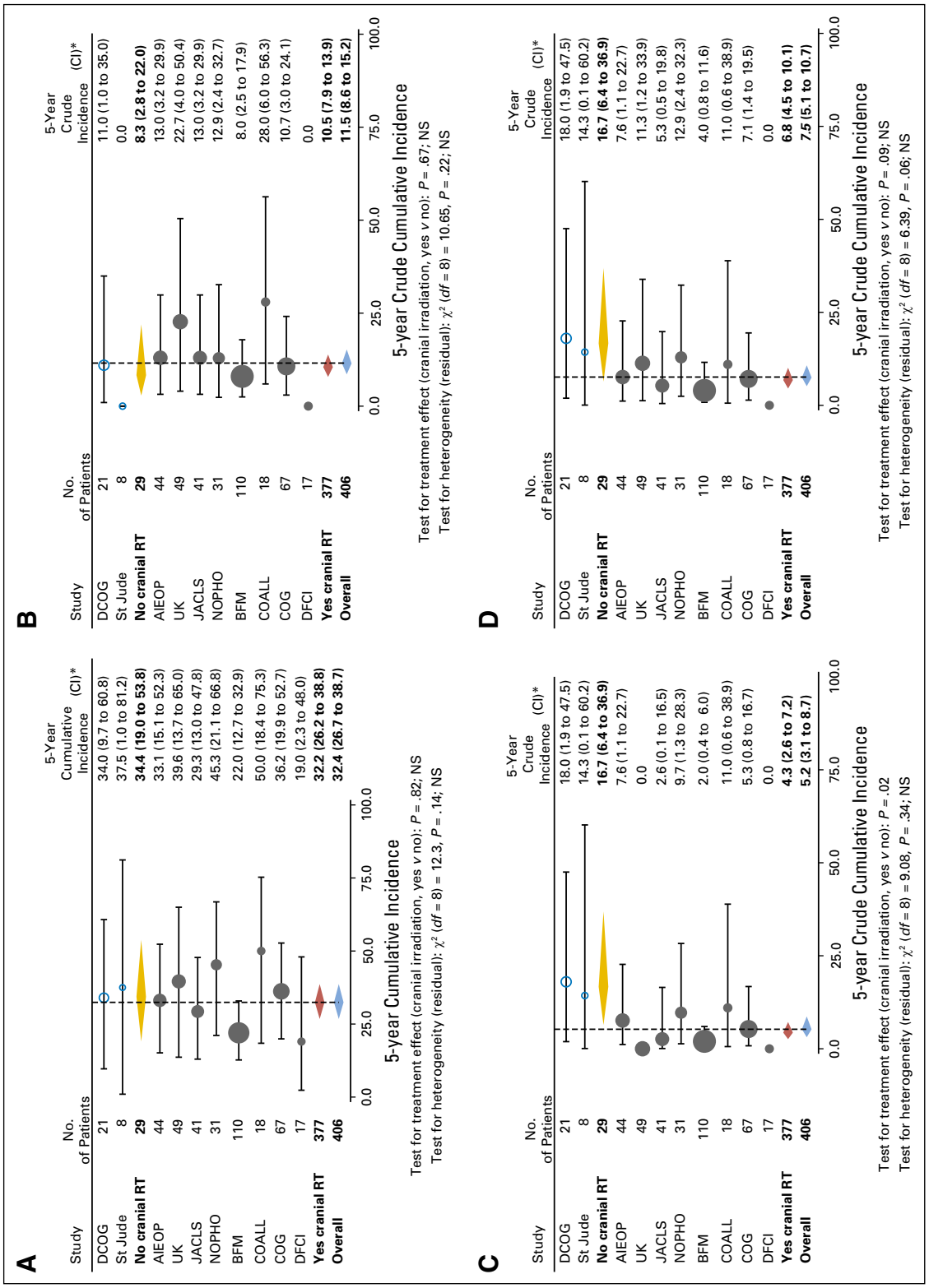

Fig 2. Five-year outcomes in the subgroup of patients with overt CNS involvement (CNS3) at diagnosis. (A) Five-year overall cumulative incidence (any event). (B) Five-year crude cumulative incidence of isolated bone marrow (BM) relapses. (C) Five-year crude cumulative incidence of isolated CNS relapses. (D) Five-year crude cumulative incidence of any CNS relapse. All forest plots present the raw cumulative 5-year estimates for each protocol, with the 99% CIs, grouped into not administering cranial radiotherapy (CRT; open blue circles) and administering CRT (gray circles). Three meta-analysis summary estimates, model based, are also presented in the form of a diamond (its width represents the 95% CIs) for protocols not administering CRT, for protocols administering CRT, and for all protocols. *CIs are 99% CIs for primary study effects and 95% CIs for summary effects. AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; COALL, Cooperative Acute Lymphoblastic Leukemia Group; COG, Children's Oncology Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute; JACLS, Japanese Childhood Leukemia Study Group; NOPHO, Nordic Pediatric Hematology and Oncology Study Group; NS, not significant; UK, United Kingdom and Ireland Group.

Table 3. Five-Year Summary Outcomes From Meta-Analyses According to Pre-emptive CRT for Subgroups Other Than CNS3 at Diagnosis

Outcome	B Cell, WBC > 100 × 10^9/L			T Cell, WBC > 100 × 10^9/L			B Cell, Slow Early Response			T Cell, Slow Early Response		
	CRT			CRT			CRT			CRT		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
5-year cumulative incidence, %												
Death (100% minus survival)	21.6	17.5	.49	27.2	19.0	.15	12.0	16.5	.36	36.3	24.7	.02
Any event (100% minus EFS)	37.0	27.4	.08	34.3	24.4	.08	22.0	26.0	.48	46.4	35.4	.19
BM relapse	17.4	15.6	.67	7.6	8.4	.88	13.2	14.7	.61	14.7	12.4	.65
Isolated CNS relapse	1.6	3.3	.32	5.4	6.6	.69	0.9	1.8	.40	4.5	2.8	.44
Any CNS relapse	3.8	6.0	.35	11.0	10.0	.77	1.9	3.8	.19	8.6	4.2	.25
No. of studies	3	6		7	3		2	5		4	4	
No. of patients	141	594		596	248		300	652		353	166	

NOTE. Even though it is not indicated for the subgroup overall, some patients within the subgroup received CRT for specific indications (eg, CNS3 or slow early response or minimal residual disease high-risk status in AIEOP-BFM 2000).
Abbreviations: AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; BM, bone marrow; CNS3, overt CNS involvement; CRT, cranial radiotherapy; EFS, event-free survival.

(Table 3), the number of patients in this category was relatively small (n = 166), and thus, it is unlikely to represent a clinically meaningful difference.

After accounting for pre-emptive CRT, significant residual heterogeneity of the incidence of CNS relapses among trials can only be attributed to other differences among treatment protocols and/or differences in the study populations. Residual heterogeneity (ie, variability across studies not caused by CRT or random error) was not present in the subgroup of patients with CNS3 at diagnosis (Fig 2, both isolated and any CNS relapses). Thus, the observed difference in outcome can be attributed to CRT rather than other differences in treatment approaches between trials.

DISCUSSION

Our meta-analysis of more than 16,000 patients recruited onto recent trials of 10 cooperative childhood ALL groups from around the world demonstrates that use of CRT in first-line therapy did not account for the observed differences in outcomes between these trials. Along with results of previous meta-analyses[10,14] and single-group studies,[2,3,12,13] the results of this study strengthen the case against use of CRT in first-line treatment of almost all subgroups of children with ALL. The only subgroup for which CRT led to a reduction in the rate of isolated or any CNS relapse was the approximately 2% to 3% of patients with ALL with CNS3 at the time of diagnosis. Although CRT was associated with a reduced risk of isolated or any CNS relapse for these patients, there was no effect on the incidence of overall events or survival. A third of patients had an event regardless of whether CRT was indicated in the protocol. Recent practice has been to limit irradiation to the cranial area, whereas in the past, the radiation field included the spine. It is uncertain whether craniospinal irradiation might be more effective than CRT in prevention of CNS relapses but would likely compromise systemic therapy delivery and increase late effects significantly. In addition, isolated CNS relapse is often associated with minimal residual disease (MRD) in the marrow and, as such, may be a herald for a systemic relapse. Treatment that only prevents CNS relapse may be associated with increased rate of systemic relapses as occurred in the Children's Cancer Group 1952 trial, which compared triple-agent (methotrexate, hydrocortisone, and cytarabine) with single-agent (methotrexate) intrathecal therapy. Although triple-agent intrathecal therapy reduced CNS relapses, there was an increase in systemic relapses, particularly in those with T-ALL, which were more difficult to salvage, resulting in an inferior overall survival for the triple-agent intrathecal group.[29]

There are several limitations to our study. First, CRT was not a randomly assigned intervention in any of the trials included in this analysis; thus, we were only able to summarize the incidence of events in groups of trials that either did or did not administer CRT. Second, the background treatment varied considerably among trials, and this could have masked or diluted the potential benefit of CRT when testing the difference in outcome between the two groups of trials. However, our comparisons are within subgroups of high-risk patients, which were well defined so that their baseline relapse risk was not expected to greatly vary among trials, limiting the potential for confounding. Third, we did not perform an individual patient data meta-analysis because of the large number of patients involved in these trials. However, the outcome estimates for all trials were not approximated from published literature, but provided by each group with a common time point and with a common definition. Fourth, censoring the follow-up at time of SCT may have introduced a bias, but the percentages of patients who received transplantations were small and unlikely to have a major influence on the results. Fifth, in the AIEOP-BFM and Japanese Childhood Leukemia Study Group studies, despite CRT not being indicated for a particular subgroup, some patients within that subgroup received it for another indication. For example, CRT was not indicated for B-cell ALL and WBC count greater than 100 × 10^9/L, but some patients within this subgroup received it because of a poor prednisolone response or MRD high-risk status. The relatively small number of patients involved should limit the influence, if any, on the analysis of outcomes for those subgroups. Finally, the sample size of individual cooperative groups was small for some subgroups of patients, reflected in the wide CIs around the estimated incidences.

As a result of similar limitations of other studies and lack of a recent randomized trial on the matter, some study groups remain

concerned about a higher risk of CNS relapse for some subgroups, such that these remain indications for CRT in their ongoing trials. However, the rate of CRT used by all groups has decreased substantially in the past two to three decades and continues to decrease. In the current AIEOP-BFM ALL 2009 study, approximately 10% of patients receive prophylactic CRT. In the current COG studies, prophylactic CRT is given only to the 2% to 3% of patients with CNS3 status and approximately 10% of patients with T-ALL with high levels of minimal residual disease after 3 months of therapy. In the current DFCI Consortium study, approximately 20% of patients (all patients with T-ALL and patients with B-cell precursor ALL with CNS3, high level of MRD at the end of remission induction, *MLL* rearrangement, or low hypodiploidy) receive CRT. In the next DFCI study, only CNS3 status will be used as a criterion for CRT for patients with B-cell ALL. In the current Cooperative Acute Lymphoblastic Leukemia (COALL) 08-09 study, CRT 12 Gy is given to approximately 6% of the patients. Only patients with CNS3 status receive CRT in the current trial of the Japanese Pediatric Leukemia/Lymphoma Study Group.

Some groups have omitted prophylactic CRT altogether in their first-line treatment protocols. The Dutch group omitted prophylactic CRT in all patients in 1997 in their ALL-9 study.[12] In the current Dutch Children's Oncology Group 11 trial, none of the patients receive prophylactic CRT with the exception of approximately 1% of patients who have high-risk ALL on the basis of MRD, are older than age 3 years, and are not eligible for allogeneic SCT. In the current Nordic Society of Hematology and Oncology study, none of the patients will receive prophylactic CRT. With the exception of 5% to 6% of patients who receive transplantation in first CR, none of the patients in the European Organisation for Research and Treatment of Cancer study will receive CRT. In the recent UKALL trials (1999 to present), CNS3 was the only indication for CRT (20 Gy), and since 2009, CRT has been further restricted to patients with persistent blasts in the CSF after two courses of intrathecal methotrexate.[13] St Jude Children's Research Hospital has omitted prophylactic CRT since 1998, beginning with the Total Therapy Study XIV. In the current Total Therapy Study XVI,[30] triple-agent intrathecal therapy is further intensified in small subgroups of patients identified to be at risk for CNS relapse in the Total Therapy Study XV, which omitted prophylactic CRT in all patients.[3]

In summary, our meta-analysis suggests that CRT is of no benefit in prevention of relapse after contemporary first-line therapy except for a small subgroup of patients with overt CNS disease at diagnosis for whom CRT reduced isolated CNS relapse but did not affect overall survival, which was poor with or without CRT. Future trials should study ways of improving the outcome for this poor-risk subgroup.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy

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