Leukemia. Author manuscript; available in PMC 2010 August 01.

Published in final edited form as:
Leukemia. 2010 February ; 24(2): 450–459. doi:10.1038/leu.2009.264.

Temporal changes in incidence and pattern of central nervous system relapses in children with acute lymphoblastic leukaemia treated on four consecutive Medical Research Council Trials, 1985–2001

Shekhar Krishnan[1,‡], **Rachel Wade**[2,‡], **Anthony V Moorman**[3], **Chris Mitchell**[4], **Sally E Kinsey**[5], **TOB Eden**[6], **Catriona Parker**[1], **Ajay Vora**[7], **Sue Richards**[2], and **Vaskar Saha**[1,6]

[1]Cancer Research UK Children's Cancer Group, Paterson Institute for Cancer Research, University of Manchester, Manchester, UK

[2]Clinical Trial Service Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, UK

[3]Leukaemia Research Cytogenetics Group, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK

[4]Paediatric Haematology/Oncology, John Radcliffe Hospital, Oxford, UK

[5]Paediatric Haematology/Oncology, St James University Hospital, Leeds, UK

[6]Academic unit of Paediatric and Adolescent Oncology, University of Manchester, UK

[7]Department of Haematology, Sheffield Children's Hospital, Sheffield, UK

Abstract

Despite the success of contemporary treatment protocols in childhood acute lymphoblastic leukaemia (ALL), relapse within the central nervous system (CNS) remains a challenge. To better understand this phenomenon, we have analysed the changes in incidence and pattern of CNS relapses in 5564 children enrolled on four successive MRC-ALL trials between 1985 and 2001. Changes in the incidence and pattern of CNS relapses were examined and the relationship with patient characteristics assessed. Factors affecting post-relapse outcome were determined. Overall, relapses declined by 49%. Decreases occurred primarily in non-CNS and combined relapses with a progressive shift towards later (≥30 months from diagnosis) relapses ($p<0{\cdot}0001$). Although isolated CNS relapses declined, the proportional incidence and timing of relapse remained unchanged. Age and presenting white cell count were risk factors for CNS relapse. On multivariate analysis, the time to relapse and the trial period influenced post-relapse outcomes. Relapse trends differed within biological subtypes. In *ETV6-RUNX1* ALL, relapse patterns

Correspondence to: Prof. Vaskar Saha, Paediatric and Adolescent Oncology Unit, Christie Hospital, Manchester M20 4BX, United Kingdom. Tel: +44 161 446 3094 Fax: +44 161 446 3092, vsaha@picr.man.ac.uk.
‡These authors contributed equally to the paper

Author contributors

VS conceived and designed the study. SK, RW, CP, VS and SR analysed data. AM provided cytogenetic data. CM, SEK, TOBE and AV were trial coordinators and reviewed the final draft. VS and SR interpreted the analysed data. SK, RW, SR, AV, AM, TOBE and VS wrote the paper.

Disclosures

The Medical Research Council, which funded these studies, had no role in the study design or in the collection, analysis or interpretation of data. All authors had full access to study data and all shared in the decision to submit for publication.

Conflict of interests

All authors declare no conflicts of interest.

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mirrored overall trends while in High Hyperdiploidy ALL, these appear to have plateaued over the latter two trial periods. Intensive systemic and intrathecal chemotherapy have decreased the overall CNS relapse rates and changed the patterns of recurrence. The heterogeneity of therapeutic response in the biological subtypes suggests room for further optimisation using currently available chemotherapy.

Keywords

childhood acute lymphoblastic leukemia; relapse; CNS; UK

Introduction

Over the last three decades, survival of children with acute lymphoblastic leukaemia (ALL) has improved from around 50%1 to nearer 80%.2 During the same period the outcome for those who relapse has remained poor.3-9 Relapses result when evolutionary pressures of frontline therapy favour emergence of a subclone from within the original blast population.10 The incidence and pattern of relapses thus vary according to protocols used. Irrespective of frontline treatment, relapsed ALL is characterised by two recurring features. The first is the critical prognostic impact of the duration of first remission (CR1).3,7-9,11 Patients who relapse within 18 months of initial diagnosis have a significantly worse outcome when compared to those with later relapses. The second is the predilection for relapse in extramedullary sites, particularly the central nervous system (CNS). At initial diagnosis, <2% of children have disease within the CNS. This can rise to 40% at first relapse.3,7,9 CNS relapses may occur isolated or in conjunction with marrow disease (combined relapse) - therapy outcomes appear to differ in these two groups. In a Children's Oncology Group (COG) report of standard risk ALL relapses, overall survival was better in children with isolated extramedullary rather than combined relapse.8 The advent of sensitive molecular investigations has complicated the distinction between these two relapse categories. For instance, the Berlin-Frankfurt-Münster (BFM) group observed that ~80% of those with apparent isolated CNS relapse had molecular evidence of marrow disease. The numbers may be small and not adjusted for the duration of CR1 but the BFM observations also indicate a poorer outcome in extramedullary relapses with concomitant higher marrow tumour burden.12

We do not know why relapses occur in the CNS. Within the limitations of our understanding, modern ALL protocols are designed to limit CNS relapses. Over the last 3 decades in the UK and elsewhere, intrathecal chemotherapy has replaced cranial irradiation as CNS-directed prophylaxis for most children with ALL.13 Along with progressive intensification of systemic therapy, these measures have in general been successful and the overall incidence of CNS relapses has steadily declined.2 Nevertheless, CNS relapse remains a significant preventable and therapeutic challenge. What then has been the impact of modern therapies on the pattern of CNS relapses in childhood ALL? Have we reached the end of optimisation with conventional drugs or is there room for further refinement of existing therapy? To answer these questions we have analysed the trends in incidence and outcome of CNS relapses among children treated for ALL in the UK over a 17-year period spanning 4 trial eras. The 5-year event free survival (EFS) improved from around 60%14 to nearly 80%15 during this period.

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Patients and Methods

Patients

All patients, treated on national protocols for childhood ALL between 1985 and 2001 and who experienced a relapse in the CNS, were included in these analyses. Patients with a non-CNS relapse (n-CNSr) were included for comparison. For purposes of this study, an isolated CNS relapse (i-CNSr) was defined as the presence of ≥5 white blood cells (WBC) per μl in cerebrospinal fluid with blasts identified on cytospin, or a biopsy-proven recurrence in the CNS or eye, in the absence of morphological disease in the bone marrow. A combined relapse (c-CNSr) was defined as the presence of CNS disease with ≥5% blasts in the bone marrow aspirate. Patients aged 1–9·99 years at presentation with diagnostic WBC counts $<50\times10^9$/L were designated NCI (National Cancer Institute) Standard Risk; all other patients were classified as NCI High Risk. Relapses were categorised as very early, early or late based on time to relapse from first diagnosis, i.e. <18 months, 18–30 months or ≥30 months respectively.

Clinical Trials

The Medical Research Council (MRC) clinical trials that ran during this period have previously been reported and include chronologically, UKALLX,16 UKALLXI,17,18 and ALL97.15,19 A major amendment was made to ALL97 in 1999 and the second phase of this trial is analysed separately (ALL97/99).20 Salient relevant differences between the trials are outlined in Table 1 and in the Supplemental. For purposes of analyses, patients have been grouped according to category of relapse (i-CNSr, c-CNSr or n-CNSr), NCI risk group, time to relapse and immunophenotype.7 Analyses were censored to the annual follow-up of 30th April 2007 for UKALLX and UKALLXI and to 31st October 2007 for ALL97 and ALL97/99. The small numbers of patients lost to follow-up were censored at the date of last contact. Median follow-up from commencement of treatment for UKALLX is 18·6 (range 0·0–22·3) years, for UKALLXI is 13·0 (range 0·3–16·6) years, for ALL97 is 9·3 (range 3·5–10·8) years and for ALL97/99 is 6·6 (range 2·3–8·0) years.

Cytogenetic and molecular genetic characterisation

Diagnostic cytogenetics was performed at regional laboratories and karyotypes were confirmed centrally.21 Some UKALLXI patients treated after 1994 were screened for *ETV6-RUNX1* fusion using reverse transcriptase polymerase chain reaction.18 Fluorescent *in situ* hybridization (FISH) analyses for *ETV6-RUNX1* and other translocations became routine from the start of ALL97. High hyperdiploidy (HH) was characterised by karyotyping (51–65 chromosomes) or by centromere FISH (using the Multiprobe-I system or by detection of classic trisomies).22 Patients were classified as having an *MLL* rearrangement if an established 11q23/*MLL* translocation was seen on karyotyping or if a split signal pattern was observed using a breakapart *MLL* FISH probe.

Statistical Methods

Analyses of relapse excluded patients who died without attaining remission. Differences in clinical features, cytogenetics and proportions of relapses between patients enrolled on the distinct protocols were analysed by the chi-squared test. The long follow-up means that analyses using simple proportions are equivalent to competing risk cumulative incidence calculations. These proportions indicate the number of patients experiencing an event of interest given the level of competing events and, when added for the different relapse categories, provide the total relapse rate. Kaplan-Meier life tables were constructed for survival curves and trials were compared using the log-rank test. Patients were censored at events other than the one of interest. Secondary malignant neoplasms (SMNs) were included

in EFS estimations (Table 1) and all post-SMN ALL relapses (overall, 3) were included in the analyses. Overall survival (OS) post relapse was defined as the time between first relapse and death from any cause. Univariate analyses using log-rank tests were performed to examine the significance of a number of variables in relation to risk of relapse and overall survival. Multivariate Cox regression analysis was used to determine factors independently associated with outcome. Both methods of analysis (proportions and Kaplan-Meier) provide different information and both have thus been presented.23 All p-values quoted are two-sided. Analyses were carried out using SAS statistical software, version 9·1 (SAS Institute Inc, Cary, NC, USA), and in-house programs.

Results

A total of 5637 children with ALL were enrolled in MRC clinical trials in childhood ALL throughout this 17-year period (1985–2001). 73 (1·3%) failed to achieve remission and are excluded from further analyses (Table 1). Of the 5564 evaluable patients, 1748 (31%) experienced relapse of whom 1168 (67%) were n-CNSr, 273 (16%) were c-CNSr and 307 (18%) were i-CNSr (Table 2). 93 (1·7%) had CNS disease at original diagnosis, of whom 27 subsequently relapsed.

Change in incidence and pattern of CNS relapses with protocols

During this period, both EFS and OS have improved with significant declines in both CNS and non-CNS relapses (Figure 1A-C and Table 2). Among those who relapsed in the CNS, the proportion with c-CNSr has fallen (p = 0·0001) while the proportion of i-CNSr has remained relatively unchanged (p = 0·8) (Table 2).

Change in time to CNS relapse with protocols

Along with the decrease in relapse rates, the duration of CR1 prior to relapse has also changed (Table 3). As the lowest relapse rates were seen with ALL97/99, a comparison has been made between ALL97/99 and all previous trials. Among relapsing patients, while the proportion of very early relapses is similar for pre-ALL97/99 and ALL97/99, there has been a drop in the proportion of early relapses, and an increase in late relapses (p<0·0001). This change in the timing of relapse with trials is also seen in c-CNSr (p=0·01) and n-CNSr (p=0·0004), but not in i-CNSr (p=0·5).

Factors influencing risk of CNS relapse

Table 4 shows the influence of risk factors on recurrence. Age, WBC count and NCI risk group were significant risk factors across all relapse categories. Unlike n-CNSr, gender was not a risk factor for CNS relapse. Immunophenotype influenced i-CNSr and n-CNSr but not c-CNSr. When analysed by trial, there were no differences in the effect of risk factors, with two exceptions (data not shown). First, the effect of gender on n-CNSr differed significantly by trial protocol (p(heterogeneity)=0·0001), with the greatest effect seen in the earlier trials. Second, while there was a suggestion that the effect of the T-cell immunophenotype on i-CNSr differed with trial (p(heterogeneity)=0·02), this was no longer observed when the less-than-robust data from UKALLX was excluded from the analyses (p=0·6).

We have sufficient data to analyse the pattern of relapses in the four main cytogenetic subtypes (Table 5). There was a significant decrease in relapse rates in *ETV6-RUNX1* patients over successive protocols (p<0·0001). The change in pattern was similar to that observed for the whole group, i.e. a proportionate decrease in c-CNSr but not in i-CNSr with time. Patients with HH ALL also showed a significant decline in relapse rates (p<0·0001), primarily between UKALLXI and ALL97. Unlike in *ETV6-RUNX1* patients, there was no apparent change in relapse pattern, with the proportion of i-CNSr and c-CNSr remaining

essentially unchanged over the trials (Table 5). Although numbers were small, there were also suggestions of a decrease in relapse rates over time in those with *MLL* (p(trend)=0·009) and t(9;22) (p(trend)=0·05) rearrangements. A decline in i-CNSr was seen in t(9:22) disease, with none observed in the later trials. However increasingly with trials, patients with adverse cytogenetic subtypes received an allograft in CR1 and thus in ALL97 and ALL97/99 most patients with t(9;22) and *MLL* rearrangements would have been transplanted.24

Outcome following CNS relapse

Similar to the COG experience,8 the overall outcome was significantly better in patients with i-CNSr (p=0·04)(Supplemental). Supplementary Figure S1A-C shows differences in post-relapse OS in each relapse category by trial. There were excess relapses in UKALLXI (Table 2) but many patients were subsequently salvaged. Excluding UKALLXI, there is no significant difference in post-relapse OS for UKALLX, ALL97 and ALL97/99. The 5-year OS post c-CNSr in UKALLX and ALL97/99 are comparable. While OS post n-CNSr appeared to be better, and for i-CNSr worse in ALL97/99, when compared to UKALLX these differences are not statistically significant.

The prognostic significance of a number of variables in relation to outcome post relapse is shown in Table 6. Univariate analyses showed that time to relapse, WBC count, adverse cytogenetics and NCI risk group were predictive of OS for all categories of relapse. As with n-CNSr, age and HH were predictive for OS in i-CNSr while immunophenotype and the *ETV6-RUNX1* genotype significantly influenced post-relapse OS in c-CNSr. Multivariate analysis, after exclusion of cytogenetic subtypes due to small numbers and missing data, confirmed the independent prognostic impact of time to relapse on post-relapse OS in all three relapse categories. Additional factors independently and significantly associated with post-relapse OS were WBC count (i-CNSr and n-CNSr) and the blast immunophenotype (c-CNSr and n-CNSr).

Besides time to relapse, multivariate analysis indicated that the trial period significantly influenced post-relapse OS across all relapse categories. The choice of steroid in frontline therapy has been reported to influence outcome.15 Overall, EFS was significantly higher with frontline dexamethasone treatment (Table 1), although within trials, this effect was observed in ALL97 and not in ALL97/99. However, frontline steroid therapy had no significant influence on OS in relapsed patients who were randomised to receive either prednisolone 40mg/m^2 (n=280) or dexamethasone 6·5mg/m^2 (n=120) in frontline protocols (p=0·4). This was equally true for post-relapse OS in each relapse category [p(heterogeneity)=0·2)] although numbers in these subgroups were small.

Transplantation

The proportion of patients treated with an allogeneic stem cell transplant (SCT) has decreased progressively with each trial (p<0·0001) as has the proportion of transplants carried out post relapse over time, p(trend)=0·0007 (Supplementary Table S1). There was no significant variation in the proportion of patients receiving a transplant post i-CNSr or n-CNSr over the study period. There was a decrease in SCT for those with c-CNSr (p=0·02), although numbers are small for ALL97/99. In patients transplanted post CNS relapse (i-CNSr or c-CNSr), two-year OS, defined from the date of transplant, was 46% (95% CI: 34%–58%) in UKALLX, 64% (56%–72%) in UKALLXI, 55% (40%–70%) in ALL97 and 65% (40%–90%) in ALL97/99. Comparison of outcome between patients treated with chemotherapy only and those treated with SCT has not been attempted due to the inherent bias in therapy selection.

Discussion

Our analyses confirm that current UK therapy for ALL is effective in preventing extramedullary relapses in most children. This does not adequately explain why the decline in CNS relapses is seen predominantly in combined relapses or the proportionately little change in the pattern of i-CNSr with progressive trials.

Though UKALLXI investigated different CNS-directed therapies, the highest incidence of all relapses, and notably c-CNSr, were seen during this era. In UKALLX all children received cranial irradiation and an anthracycline during induction.16 In ALL97/99, anthracyclines were only given to NCI high risk patients or those with poor early response to therapy15,20 and radiotherapy was reserved for those with CNS disease at diagnosis. Nevertheless there is a significant decrease in relapse rates in all categories in ALL97/99. Thus CNS recurrence can largely be prevented without the use of high dose methotrexate or cranial irradiation. The more frequent use of intrathecal methotrexate is contributory, but as this was introduced in UKALLXI, it is not the sole factor. In ALL97 and ALL97/99, steroid therapy was randomised between prednisolone and dexamethasone. The latter is thought to have better penetration into the CNS. While significant improvements in EFS and in both CNS and non-CNS relapse rates were seen with dexamethasone, there was no difference in OS.15 Additionally, there was no significant heterogeneity of effect of the randomised steroid on outcome by trial. Thus other chemotherapeutic changes in ALL97/99 are primarily responsible for the improvement in outcome between ALL97 and ALL97/99. In ALL97/99, UKALLX/ALL97 intensification phases were replaced with BFM-type consolidation blocks, therapy was risk stratified and intrathecal therapy extended. The duration of therapy for boys was extended to 3 years, so that from 1998, most boys received 3 instead of 2 years of therapy. The additional randomisation of 6-mercaptopurine with 6-thioguanine (6-TG) found the latter to be protective against i-CNSr, but also hepatotoxic.19 Although synergy with dexamethasone is a possibility, neither 6-TG nor its active metabolites cross the blood brain barrier.19 Thus the evidence suggests that risk-stratified intensification of systemic therapy along with frequent intrathecal chemotherapy is the most successful approach to prevention of CNS relapse. A similar observation has been reported by COG in the CCG-1961 study. Children receiving early post induction intensification of therapy showed a significant decrease in n-CNSr and c-CNSr but not i-CNSr.25

Thus both intensification and more frequent intrathecal therapy appear to have played a role in the decline in CNS relapses. With multi-agent chemotherapy, it is difficult to identify the key responsible agent(s). The differential relapse trends in the cytogenetic subtypes offer room for speculation. In patients with *ETV6-RUNX1*, the incidence of relapses has progressively decreased with each successive protocol from UKALLXI onwards. Further decline in *ETV6-RUNX1* associated relapses in ALL97/99 occurs primarily in the c-CNSr group. We have already commented on the fact that the improvement in outcome with ALL97/99 cannot be attributed to dexamethasone alone. *ETV6-RUNX1* leukaemias are thought to benefit from intensive asparaginase therapy.26,27 UKALLXI and ALL97 used suboptimal doses of Erwinase. The improved outcome of *ETV6-RUNX1* patients in ALL97/99 is probably related to the more effective use of *E. coli* asparaginase (Elspar®, Merck, USA) in this trial. The additional intensification of asparaginase therapy in ALL2003 is expected to further reduce *ETV6-RUNX1* relapses. In HH ALL, a predilection for extramedullary relapses in patients treated on contemporary chemotherapy regimens has been reported from a single centre.28 Though relapses in HH patients halved in ALL97, ALL97/99 provided no apparent further benefit and overall, the proportion of i-CNSr and c-CNSr has remained the same over trials. HH ALLs are more likely to be responsive to intensive methotrexate regimens.28 In UKALLXI, high dose intravenous methotrexate (HDMTX) was found to be protective against i-CNSr.13 The relapse rate for HH is also

lower in this protocol than that for *ETV6-RUNX1*. It is thus tempting to postulate that outcome in patients with HH may be further improved by the targeted reintroduction of HDMTX in future trials. Thus, there are still opportunities to biologically adapt current therapy to improve outcomes.

Though the incidence of relapse has decreased with time, post-relapse outcomes have not improved. This suggests that by optimising treatment, we are now preventing relapses in those who were earlier cured with salvage therapy. Given our incomplete understanding of why CNS relapses occur and the paucity of new agents, the best therapeutic strategy remains unclear. The results of transplantation in children with i-CNSr relapses have been variable.7,8,11,30-32 In retrospect, a number of children who were transplanted for disease recurrence in earlier trials would have been cured by current chemotherapy. The standard approach for those who are not transplanted is chemoradiotherapy. However, there is little consensus on the dose, type and timing of CNS irradiation.2 Radiotherapy no longer has a role in preventing CNS relapses in frontline therapy. Is it really of benefit as a therapeutic adjunct to systemic chemotherapy in relapsed disease? This is a difficult question to answer as the small numbers and heterogeneity of disease preclude a randomised approach to this problem. At the moment the most effective strategy remains prevention of disease recurrence. Our analyses suggest that both the biological heterogeneity of the disease and combined systemic and intrathecal chemotherapy influence the incidence and pattern of CNS relapse. Thus further optimisation with currently available agents is possible and may further decrease CNS recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge the enormous contributions of Professors Judith Chessells, John Lilleyman, Frank Hill and Ian Hann as well as members of the Leukaemia Lymphoma Division, Children's Cancer and Leukaemia Group during this period. An immense debt of gratitude is owed to all patients and parents who participated in these trials. This work is supported by grants from Cancer Research UK (VS), Leukaemia Research Fund (AM), the Medical Research Council (CM, SR, AV) and the Teenage Cancer Trust (TOBE).

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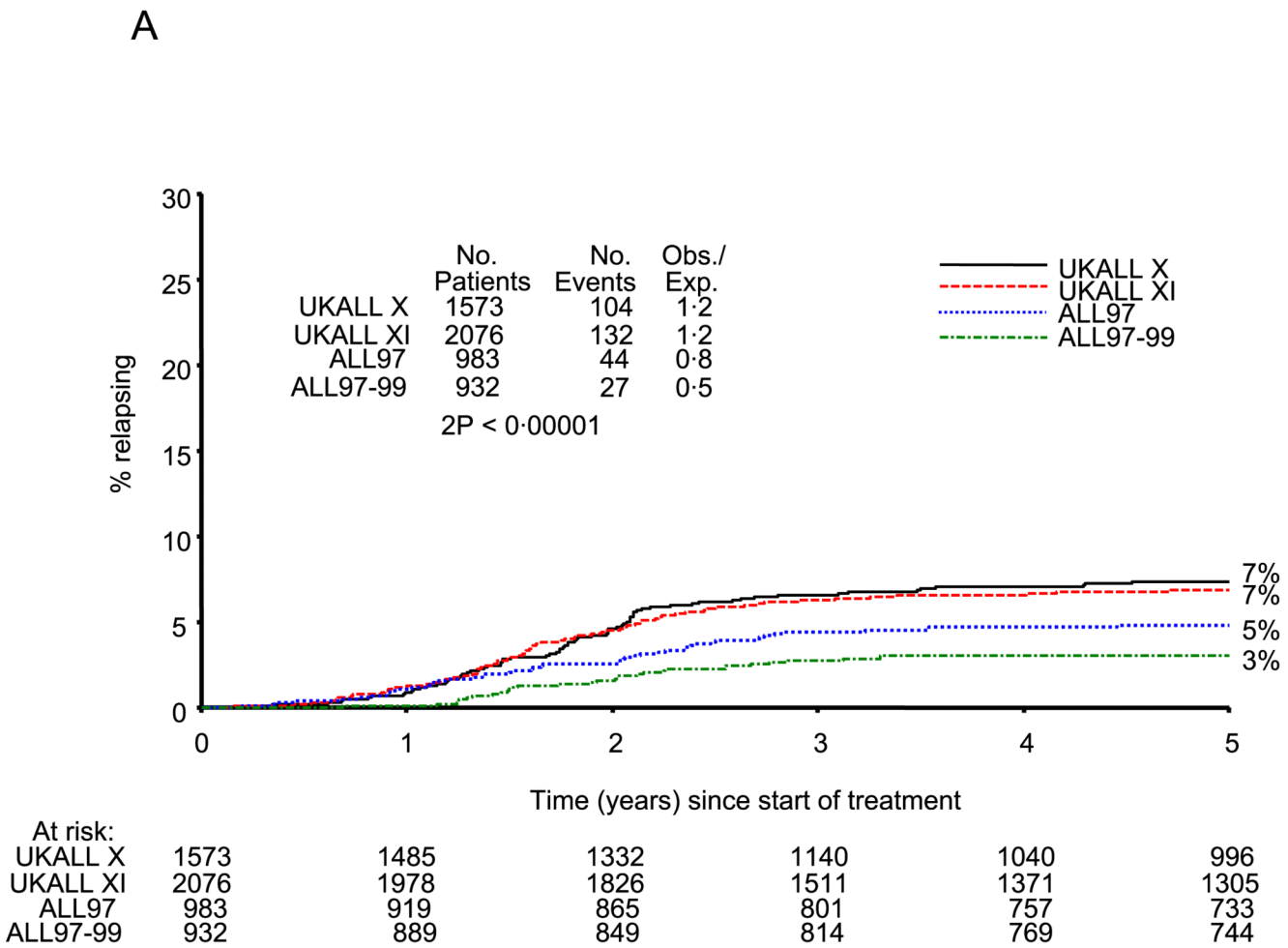

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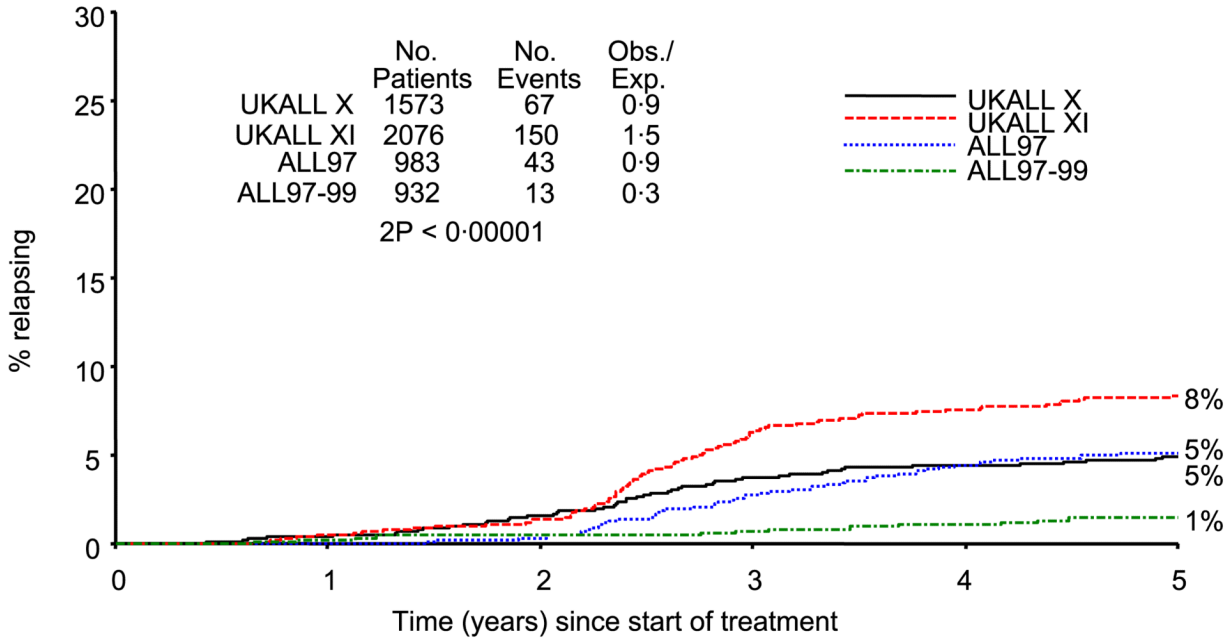

At risk:						
UKALL X	1573	1485	1332	1140	1040	996
UKALL XI	2076	1978	1826	1511	1371	1305
ALL97	983	919	865	801	757	733
ALL97-99	932	889	849	814	769	744

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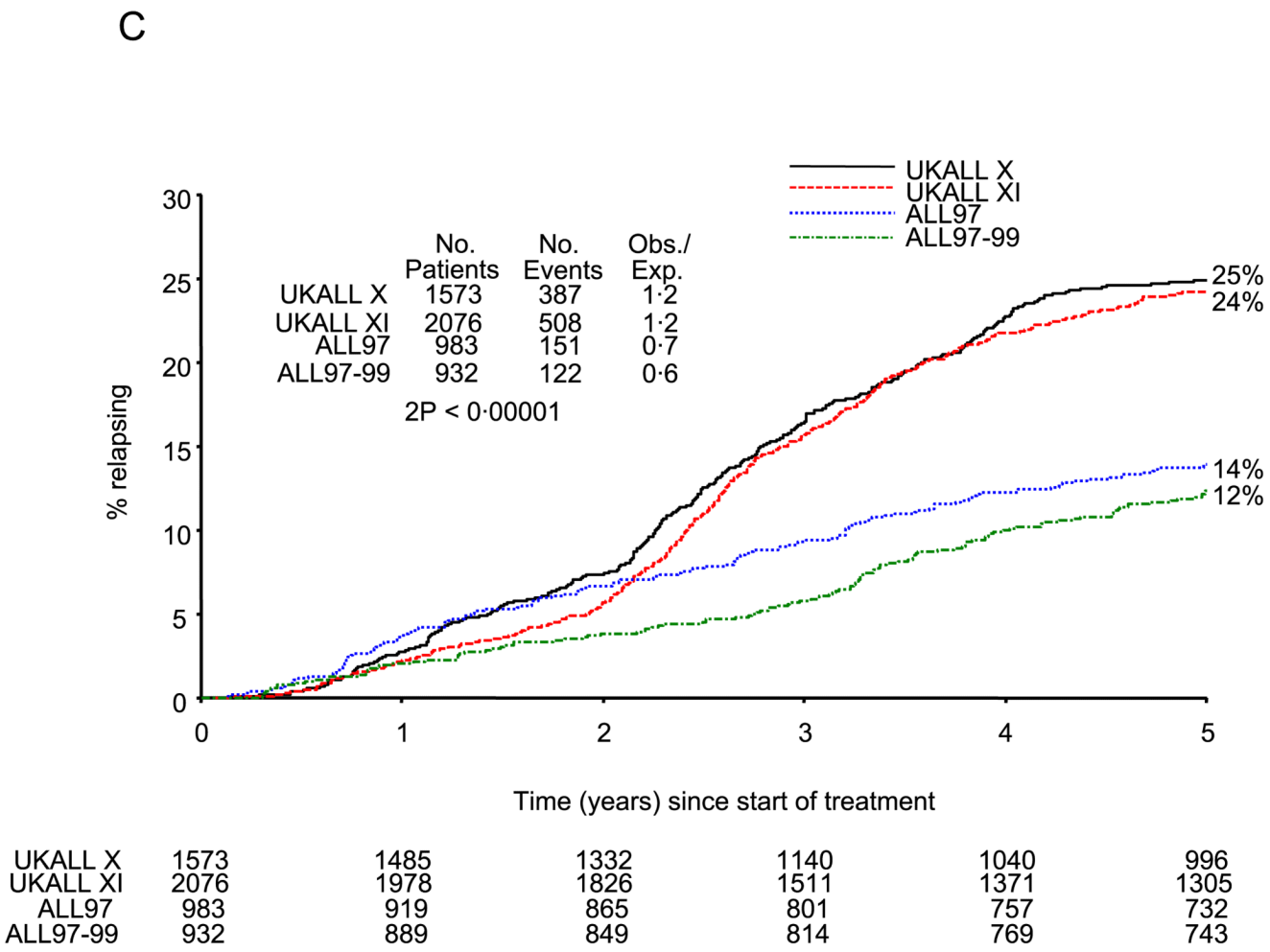

Figure 1.

Kaplan-Meier analysis of cumulative incidence of site-specific relapse censored for death in remission or alternative site of relapse. (A) i-CNSr (B) c-CNSr and (C) n-CNSr. p-values are for heterogeneity between trials.

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Table 1

Details of MRC childhood ALL trials analysed in this study. Both five-year EFS and OS have improved with trials. The proportion of boys and girls, immunophenotype, CNS disease at diagnosis and NCI risk groups are comparable between trials. The age limit of eligibility increased from ALL97 onwards and as a result, a greater proportion of older children and slightly fewer younger children were recruited to ALL97 and ALL97/99 when compared with previous trials

		UKALLX	UKALLXI	ALL97	ALL97/99
Time period		1985–1990	1991–1997	1997–1999	1999–2001
Number enrolled		1612	2090	997 (151 on HR1)	938
Number achieving CR1 (%)		1573 (97·6%)	2076 (99·3%)	983 (98·6%)	932 (99·4%)
*Survival rates (95% CI)	5 year EFS (%)	61·9	62·8	73·8	79·8
		(59·5–64·3)	(60·6–65·0)	(71·1–76·5)	(77·3–82·3)
	5 year OS (%)	77·4	84·6	83·5	88·0
		(75·8–79.0)	(83·3–85·9)	(81·5–85·5)	(86·2–89·8)
Age Eligibility (yrs)		0–14	1–14	1–17	1–17
Age at diagnosis (yrs)	<2	163 (10%)	157 (8%)	76 (8%)	63 (7%)
	2–9	1212 (75%)	1617 (77%)	716 (72%)	680 (72%)
	≥10	237 (15%)	316 (15%)	205 (20%)	195 (21%)
WBC	$<50 \times 10^9$/l	1270 (79%)	1628 (78%)	770 (77%)	717 (76%)
	$\geq 50 \times 10^9$/l	342 (21%)	462 (22%)	227 (23%)	221 (24%)
Immunophenotype	Non T-cell	1397 (86%)	1730 (83%)	863 (86%)	831 (88%)
	T-cell	139 (9%)	206 (10%)	118 (12%)	92 (10%)
	Unknown	76 (5%)	154 (7%)	16 (2%)	15 (2%)
CNS disease at diagnosis	No	1583 (98·2%)	2059 (98·5%)	979 (98·2%)	918 (97·9%)
	Yes	29 (1·8%)	31 (1·5%)	18 (1·8%)	20 (2·1%)
≠Induction	Anthracycline	Yes	None post 1992	No	For IR and HR
	Steroid	Prednisolone	Prednisolone	Randomised	Randomised
Intensification	Intensification blocks	Randomised, none, 1 or 2 short blocks	Randomised 2 or 3 blocks	Randomised 2 or 3 blocks	2 BFM type delayed intensification blocks
Duration of treatment		2 years	2 years	2 years For boys, 3 years after 1998	Girls: 2 years Boys: 3 years
†CNS directed therapy	Randomised	No	Yes	No	No

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		UKALLX	UKALLXI	ALL97	ALL97/99
	Cranial irradiation	18 Gy for all	WBC ≥50×10^9/L:	Initially as UKALL XI	Only for CNS disease
			24 Gy or HD MTX	(XRT = 39) and later	
			WBC <50×10^9/L:	only for CNS disease	
			HD MTX or IT MTX		
	IV MTX	No	HD MTX	No	Capizzi for HR patients
	Continuing IT MTX	No	For those without cranial irradiation	Yes	Yes
Deaths in CR1		71 (4·5%)	42 (2·0%)	34 (3·4%)	36 (3·9%)
Second Malignant Neoplasms (Deaths)		30 (18)	16 (12)	6 (2)	5 (2)
Number of patients treated with different CNS-directed therapies in UKALL XI and ALL 97					
WBC ≥50 × 10^9/l treatment received	XRT		133	39	
	HDMTX + ITMTX		160	93	
	Unknown		17	3	
	**Very high risk		152	92	
WBC ≥50 × 10^9/l randomised	XRT		186		
	HDMTX + ITMTX		188		
WBC <50 × 10^9/l randomised	HDMTX + ITMTX		754		
	ITMTX		759		

CR1 = first complete remission

*CI = confidence intervals; EFS = Event Free Survival; OS = Overall Survival. Deaths in CR1 include deaths from second malignant neoplasms.

≠For ALL97/99, IR = Intermediate Risk, children aged ≥10 years or with a presenting WBC of ≥50 × 10^9/l; HR = High Risk, adverse cytogenetics [(t(9;22), *MLL* rearrangements near-haploid or hypodiploid karyotype] or slow early response to therapy. Steroid randomisation was dexamethasone (6·5 mg/m^2) or prednisolone (40 mg/m^2).

†HD MTX = High dose intravenous methotrexate, 6–8 gm/m^2; ITMTX = intrathecal methotrexate. Capizzi = escalating doses of intravenous methotrexate with timed L-Asparaginase during interim maintenance, XRT = Cranial irradiation.

**Very high risk based on the Oxford hazard score33 or cytogenetics. In UKALLXI very high risk patients were recommended transplant and hence received total body irradiation rather than XRT or HDM. In ALL97, very high risk patients were treated on HR1.

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Table 2

Number of relapses in each relapse category by trial. i-CNSr = isolated CNS relapse, c-CNSr = combined CNS relapse, n-CNSr = non-CNS relapse. Numbers in brackets represent proportions (equivalent to competing risk cumulative incidence) within each relapse category for all patients (top) and for all relapses *[bottom in italics]*. p-values are for heterogeneity between trials

	UKALLX (n=1573)		**UKALLXI (n=2076)**		**ALL97 (n=983)**		**ALL97/99 (n=932)**		**p value (heterogeneity)**
All relapses	558	(35%)	790	(38%)	238	(24%)	162	(17%)	<0·0001
i-CNSr	104	(7%)	132	(6%)	44	(5%)	27	(3%)	0·0001
		[19%]		*[17%]*		*[18%]*		*[17%]*	0·8
c-CNSr	67	(4%)	150	(7%)	43	(4%)	13	(1%)	<0·0001
		[12%]		*[19%]*		*[18%]*		*[8%]*	0·0001
n-CNSr	387	(25%)	508	(24%)	151	(15%)	122	(13%)	<0·0001
		[69%]		*[64%]*		*[63%]*		*[75%]*	0·02

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Table 3

Changing trends in time to relapse from first diagnosis in children treated on MRC ALL protocols. A comparison is made between ALL97/99 and all other trials. Compared to earlier trials, c-CNSr and n-CNSr occur later in ALL97/99. The proportion and timing of i-CNSr remains unchanged. Numbers in brackets are percentages of total relapses in each category. p-values for heterogeneity between trials correspond to comparison of pre-ALL97/99 trials with ALL97/99

	UKALLX	UKALLXI	ALL97	pre-ALL97/99		ALL97/99		p-value
Any relapse								
Very Early (<18 mths)	139	148	71	358	(23%)	42	(26%)	<0·0001
Early (18–30 mths)	183	278	55	516	(33%)	25	(15%)	
Late (≥30 mths)	236	364	112	712	(45%)	95	(59%)	
Total	**558**	**790**	**238**	**1586**		**162**		
i-CNSr								
Very Early (<18 mths)	42	57	19	118	(42%)	10	(37%)	0·5
Early (18–30 mths)	48	58	17	123	(44%)	11	(41%)	
Late (≥30 mths)	14	17	8	39	(14%)	6	(22%)	
Total	**104**	**132**	**44**	**280**		**27**		
c-CNSr								
Very Early (<18 mths)	13	18	1	32	(12%)	4	(31%)	0·01
Early (18–30 mths)	26	59	15	100	(38%)	0	(0%)	
Late (≥30 mths)	28	73	27	128	(49%)	9	(69%)	
Total	**67**	**150**	**43**	**260**		**13**		
n-CNSr								
Very Early (<18 mths)	84	73	51	208	(20%)	28	(23%)	0·0004
Early (18–30 mths)	109	161	23	293	(28%)	14	(11%)	
Late (≥30 mths)	194	274	77	545	(52%)	80	(66%)	
Total	**387**	**508**	**151**	**1046**		**122**		

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Table 4

Log-rank analyses of variables influencing recurrence in each relapse category. O/E = Observed/Expected ratio

Variable		No. patients	i-CNSr			c-CNSr			n-CNSr		
			Observed relapses	O/E	p-value	Observed relapses	O/E	p-value	Observed relapses	O/E	p-value
Sex	Male	3166	180	1·1	0·3	166	1·1	0·05	786	1·2	<0·0005
	Female	2398	127	0·9		107	0·9		382	0·7	
WBC (× 10^9/L)	<50	4340	188	0·8	<0·00005	194	0·9	<0·00005	865	0·9	<0·0005
	≥50	1224	119	2·1		79	1·7		303	1·5	
Age (years)	<2	452	53	2·2	<0·00005	30	1·4	0·04	68	0·7	<0·00005
	2–9	4178	208	0·9	0·0006 (trend)	198	0·9	0·8 (trend)	828	0·9	<0·00005 (trend)
	10+	934	46	1·0		45	1·2		272	1·6	
NCI risk	Standard	3655	165	0·8	<0·00005	162	0·8	<0·00005	665	0·8	<0·00005
	High	1909	142	1·5		111	1·4		503	1·5	
Immunophenotype	non T-cell	4767	257	1·0	0·02	241	1·0	0·4	961	1·0	<0·00005
	T-cell	539	35	1·5		25	1·2		138	1·6	

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Table 5

Changing trends in relapses in four cytogenetic subtypes over successive trials. The rise in incidence of translocation-associated leukaemias in the later trials reflects the use of FISH screening. The proportion of children in each cytogenetic group does not differ by trial, with the exception of *MLL* rearrangements (infants included in UKALLX but not in UKALLXI). The numbers screened represent the number of patients in each trial with available cytogenetic data. Numbers in brackets represent percentages of total relapses in each group

	UKALLX	UKALLXI	ALL97	ALL97/99	p-value
ETV6-RUNX1					
Screened	No Data	663	764	869	
N (% of screened)		131 (20%)	175 (23%)	194 (22%)	0·3
Relapses		37%	17%	9%	<0·0001 (trend <0·0001)
i-CNSr		6 (19%)	3 (10%)	4 (24%)	0·1
c-CNSr		9 (12%)	9 (30%)	0	
n-CNSr		33 (69%)	18 (60%)	13 (76%)	
HH					
Screened	547	1656	862	792	
N (% of screened)	197 (36%)	528 (32%)	294 (34%)	272 (34%)	0·3
Relapses	27%	30%	16%	15%	<0·0001 (trend <0·0001)
i-CNSr	13 (24%)	26 (16%)	9 (20%)	8 (20%)	0·6
c-CNSr	6 (11%)	31 (20%)	8 (17%)	4 (10%)	
n-CNSr	35 (65%)	103 (64%)	29 (63%)	28 (70%)	
t(9;22)					
Screened	547	1656	931	903	
N (% of screened)	11 (2%)	26 (2%)	17 (2%)	26 (3%)	0·2
Relapses	64%	58%	53%	35%	0·3 (trend 0·05)
i-CNSr	3 (43%)	2 (13%)	0	0	0·1
c-CNSr	0	1 (7%)	1 (11%)	0	
n-CNSr	4 (57%)	12 (80%)	8 (89%)	9 (100%)	
***MLL* rearranged**					

	UKALLX	UKALLXI	ALL97	ALL97/99	p-value
Screened	547	1660	932	901	
N (% of screened)	15 (3%)	23 (1%)	14 (2%)	24 (3%)	0·04
Relapses	60%	65%	50%	25%	0·03 (trend 0·009)
i-CNSr	2 (22%)	0	0	2 (33%)	0·2
c-CNSr	0	3 (20%)	2 (29%)	1 (17%)	
n-CNSr	7 (78%)	12 (80%)	5 (71%)	3 (50%)	

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Table 6

Log-rank analyses of factors influencing outcome in each category of relapse (incomplete data for cytogenetic subtypes). O/E = Observed/Expected ratio

Variable		Post i-CNSr				Post c-CNSr				Post n-CNSr			
		No. patients	Deaths	O/E	p-value	No. patients	Deaths	O/E	p-value	No. patients	Deaths	O/E	p-value
Sex	Male	180	102	1·0	0·7	166	97	1·1	0·2	786	452	1·0	0·06
	Female	127	71	1·0		107	54	0·9		382	230	1·1	
WBC (× 10^9/L)	<50	188	94	0·8	0·0009	194	95	0·8	0·0003	865	461	0·9	<0·00005
	≥50	119	79	1·4		79	56	1·5		303	221	1·5	
Age (years)	<2	53	39	1·6	0·009	30	18	1·2	0·5	68	36	0·9	<0·00005
	2–9	208	109	0·9	(0·04 trend)	198	104	0·9	(0·2 trend)	829	450	0·9	<0·00005 (trend)
	10+	46	25	1·0		45	29	1·3		271	196	1·6	
NCI risk	Standard	165	82	0·8	0·003	162	77	0·8	0·001	665	325	0·7	<0·00005
	High	142	91	1·3		111	74	1·4		503	357	1·5	
Immunophenotype	non T-cell	257	142	1·0	0·4	241	127	0·9	<0·00005	961	524	0·9	<0·00005
	T-cell	35	20	1·2		25	21	2·8		138	117	2·4	
Time to relapse	<18 mths	128	83	1·3	0·0003	36	31	2·8	<0·00005	236	218	3·6	<0·00005
	18–30 mths	134	75	0·9	(trend)	100	68	1·3	(trend)	307	226	1·3	(trend)
	≥30mths	45	15	0·5		137	52	0·6		625	238	0·5	
ETV6-RUNX1	No	80	45	1·0	0·6	73	40	1·3	0·002	324	184	1·1	0·002
	Yes	13	6	0·8		18	3	0·3		64	24	0·6	
t(9;22)	No	217	112	1·0	0·01	190	96	1·0	0·04	757	432	1·0	0·01
	Yes	5	5	3·8		2	2	6·2		33	24	1·7	
HH	No	161	90	1·1	0·02	138	77	1·1	0·06	569	361	1·2	<0·00005
	Yes	56	23	0·7		49	19	0·7		195	83	0·6	
MLL rearranged	No	218	112	1·0	0·003	187	93	1·0	0·03	768	434	1·0	0·0001
	Yes	4	4	5·8		6	5	3·1		27	23	2·5	