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LETTER TO THE EDITOR

The prognostic significance of trisomy 4 in acute myeloid leukaemia is dependent on age and additional abnormalities

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It is well recognised that cytogenetics is a key prognostic factor in acute myeloid leukaemia (AML)¹ and that trisomy 4 occurs as a rare chromosomal abnormality (< 1%).^{1–3} The additional chromosome 4 may be present as a sole abnormality or occur in association with other chromosomal changes. To date the prognostic significance of trisomy 4 in AML is unclear, partly due to its rarity. Here, we examined clinical and genetical characteristics, remission rates and survival outcomes of 87 patients with AML and trisomy 4 to ascertain the prognostic significance of this abnormality.

Patients with trisomy 4 were identified among those recruited to UK-based AML treatment trials (AML10, AML11, AML12, AML14, AML15 and AML16) between May 1989 and October 2009.^{4–9} Median follow-up time for the cohort was 10.1 years (range 0.3–21.9 years). The Ethics Committee of each participating centre and R3 (Wales) approved these studies. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Cytogenetic analysis of pre-treatment bone marrow or peripheral blood was performed locally, reviewed centrally by the Leukaemia Research Cytogenetics Group and collated retrospectively. Karyotypes were reported using the International System for Human Cytogenetic Nomenclature (ISCN).¹⁰ Cases with trisomy 4 in addition to chromosomal abnormalities that we have previously defined as favourable and adverse risk¹ were removed in order to investigate the independent prognostic relevance of trisomy 4 among the intermediate risk group. As we have previously defined cases with a complex karyotype based solely on the number of chromosomal abnormalities as intermediate risk,¹¹ they were retained in the study.

To examine the effects of age, patients were divided into three groups (1–16 years (paediatric), adults < 60 years and adults 60+ years).

Survival analysis was performed on patients treated with intensive curative intent. The comparator group comprised of 5003 patients with a normal karyotype, classified as intermediate risk, treated on the same protocols. Complete remission (CR) was defined as a bone marrow aspirate with < 5% leukaemic blasts and evidence of regeneration of normal hematopoietic cells. Overall survival (OS) was calculated from the date of entry onto the trial, to death from any cause or the date of last follow-up. For those patients who achieved CR, relapse-free survival was time from CR to first event (relapse or death in CR); cumulative incidence of relapse is the cumulative probability of relapse with death in CR as a competing risk. OS/relapse-free survival/cumulative incidence of relapse percentages are quoted at 5 years. Event-free survival was defined as time from randomisation to either relapse or death in CR for patients who achieved a remission, censored at date last known to be alive in remission. Patients not achieving remission were deemed to have an event on day 1. Surviving patients were censored on 31 March 2010

Table 1. Demographic and clinical details of patients with and without trisomy 4

	Trisomy 4		P-value	
	Sole abnormality (%)	With additional abnormalities (%)		
Total	35 (40)	52 (60)		
Sex				
Male	14 (40)	26 (50)	0.359	
Female	21 (60)	26 (50)		
Age				
< 2	—	2 (4)	0.7 ^a	
2–5	—	1 (2)		
5–15	4 (11)	3 (6)		
16–25	2 (6)	4 (8)		
26–35	5 (14)	6 (12)		
36–45	3 (9)	6 (12)		
46–55	6 (17)	10 (19)		
56–65	7 (20)	9 (17)		
66+	8 (23)	11 (21)		
White Cell Count ($\times 10^9/L$) ^b				
< 50	21 (60)	44 (88)	0.04 ^a	
≥ 50	14 (40)	6 (12)		
FAB type ^c				
M0	—	10 (19)	0.116	
M1	10 (29)	8 (15)		
M2	4 (11)	1 (2)		
M3	—	—		
M4	4 (11)	4 (8)		
M5	2 (6)	4 (8)		
M6	—	—		
M7	—	—		
RAEBt	1 (3)	—		
Other	—	1 (2)		
Intensive treatment	33 (94)	46 (88)	0.6	
CR	85%	80%		
Transplants given in CR1				
Stem cell transplant	10 (36)	7 (10)	0.3	
Allograft	9 (90)	4 (57)		
Sibling	5 (46)	2 (50)		
MUD	4 (54)	2 (50)		
Autograft	1 (10)	2 (29)		
Unknown	0 (0)	1 (14)		
Relapse	9 (26)	10 (19)		
Died	13 (37)	13 (25)		
Complex				
1–3 abns	35 (100)	22 (42)		< 0.0001
≥ 4 abns	—	30 (58)		

Abbreviations: CR, complete remission; FAB, French-American-British Classification; MUD, matched unrelated donor. ^aWilcoxon rank-sum test. ^bavailable for 85 patients (98%). ^cavailable for 55 patients (64%).

(AML10/11/12/14), or 1 January 2014 (AML15/16), when follow-up was complete for 95% of patients.

Survival rates were calculated and compared using the Kaplan–Meier method, log-rank test and Cox regression. Multivariate analyses were adjusted for additional factors: age (as continuous variable), protocol (paediatric/young adult/older adult), white blood cell count, secondary disease and performance status. Effect sizes are given as odds or hazard ratios with 95% confidence intervals. Categorical data were compared using χ^2 and Mantel–Haenszel tests, and continuous variables using the Wilcoxon rank-sum test. All *P*-values were two-tailed. Analyses were performed using Intercooled Stata 13.1 for Windows (Stata Corporation, College Station, TX, USA) and SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

We identified 87 patients with trisomy 4, who were stratified as intermediate risk. Trisomy 4 was the sole cytogenetic abnormality in 35 cases (40%), while 18 (35%) had additional chromosomal gains. Among the structural abnormalities found in the remaining 34 cases (39%), the only recurrent changes were abnormalities of 12p (*n*=3). The ratio of males to females was 1:1.5 with a median age of 51 years (range 1–83 years). There was no difference in distribution by sex or age based on whether trisomy 4 was found alone or in association with other abnormalities (*P*=0.359 and *P*=0.904 respectively; Table 1).

There were no differences in demographics according to the type of additional abnormalities, both among adults in both age categories and paediatric patients (*n*=10).

The majority of adult (82%) and all paediatric patients (100%) with trisomy 4 achieved CR. OS was 35% at 5 years both in patients with trisomy 4 and comparator group (adjusted HR 1.19 (0.91–1.57) *P*=0.2). Survival appeared marginally reduced in patients with trisomy 4 as the sole karyotypic change, but did not reach significance (OS adjusted HR 1.01 (95% CI 0.56–1.82) *P*=1.0 (Figure 1), event-free survival adjusted HR 1.11 (95% CI 0.85–1.45) *P*=0.4). The survival effects of trisomy 4 alone or in association with other abnormalities were not significantly different (Figure 1). Regardless of trisomy 4 status, patients >60 years had an overall worse prognosis than the paediatric cases. There was no significant interaction between protocol and the effect of trisomy 4.

Relapse occurred in 22% of trisomy 4 patients (*n*=19), with a similar relapse rate of 54% at 5 years to the comparator group (Figure 1e), regardless of whether trisomy 4 existed alone or in association with other abnormalities (*P*=0.473). Paediatric patients with trisomy 4 were more likely to relapse than their age specific comparator group (60% vs 37%, *P*=0.06) with most relapses occurring within the first 12 months following diagnosis (Figure 1f). Although there was an observed difference in OS for

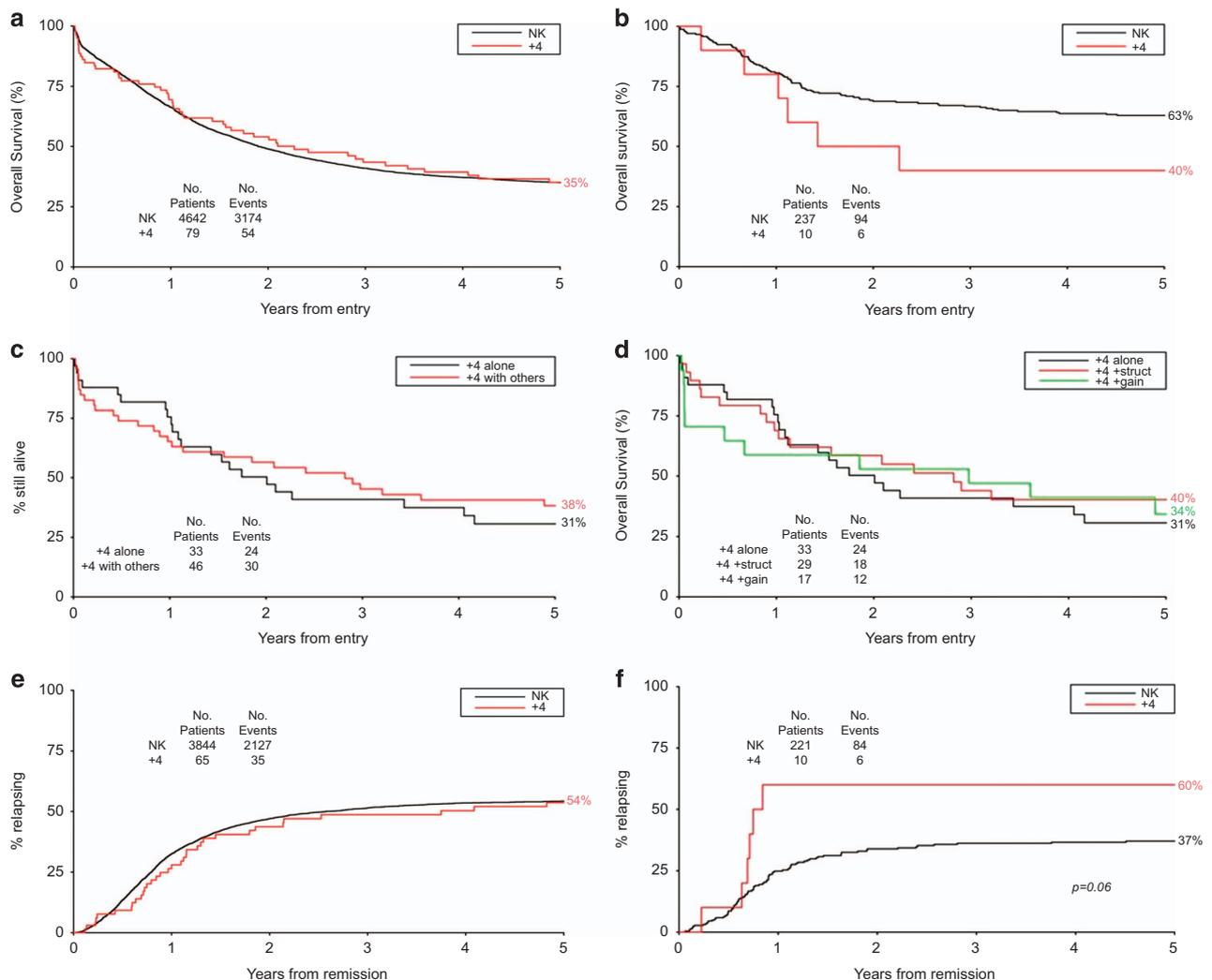


Figure 1. Kaplan–Meier survival curves demonstrating OS for AML patients with trisomy 4 compared with patients with a normal karyotype classified as intermediate risk.

the paediatric patients, it was not significant (40% vs 63% NK, $P=0.18$). Older adults had an inferior outcome (5-year OS 7% >60 years).

Trisomy 4 is a rare chromosomal abnormality in AML, occurring at an incidence of <1%. Although its prognostic relevance has been frequently debated,¹⁻³ its association to outcome remains unclear. This uncertainty is due partly to the rarity of trisomy 4 and the restriction of studies to cases in which it occurred as an isolated abnormality.¹⁻³ Here, we present the largest cohort to date, of 87 patients treated on sequential MRC-UK AML trials. As well as cases with trisomy 4 as the sole abnormality, those with additional chromosomal changes, classified as intermediate risk, were included in the study. In support of this case selection, we have recently shown that the subgroup of patients with trisomy 4 in association with the favourable risk abnormality, t(8;21)(q22;q22), maintained a high 5-year OS of 74% (Standard Error 1.5%), although an increased rate of relapse was observed compared with those patients without trisomy 4.¹² Similarly, we observed that patients with adverse risk abnormalities maintained the same poor outcome regardless of the presence of trisomy 4 (data not shown). Thus we restricted this study to cases within the intermediate risk group.

Trisomy 4 often occurs as the sole cytogenetic change. However it may also be a component of a hyperdiploid karyotype,¹¹ or associated with other structural abnormalities. We showed no significant difference in distribution or outcome based on these potential classifications. Abnormalities of 12p were the only recurrent structural changes identified. We and others have previously described 12p aberrations to be a poor prognostic marker in childhood AML.^{13,14}

Although patients in this cohort were treated on a number of trials, the regimens were similar and performed within the same institutions, thus reducing treatment bias. In this study, the outcome of trisomy 4 patients was compared with those with a normal karyotype, classified as intermediate risk, treated on the same protocols. Trisomy 4 patients responded well to induction chemotherapy with the majority in all age groups achieving remission. Their 5-year OS was intermediate, comparable to those with a normal karyotype. Outcome was similar irrespective of whether the trisomy occurred alone or in association with other abnormalities. Age is a well-known prognostic factor in AML,^{1,8} also reflected in this cohort, in which older patients, notably adults >60 years had an inferior outcome. Despite an initial good response to treatment, patients with trisomy 4 were susceptible to relapse. In adults the relapse rate was similar to other patients with an intermediate risk profile. However paediatric patients with trisomy 4 had a significantly higher relapse rate than adults with the same abnormality, occurring within the first year following diagnosis. Although patient numbers in this study were small, the increased rate of relapse was significant. As OS was not different from those with a normal karyotype, these observations suggest that trisomy 4 patients are being salvaged by relapse therapy.

It has previously been suggested that *c-KIT* mutations (located to 4q12) may influence the function of trisomy 4 in leukaemogenesis.^{2,3,15} Although mutation data were not available for these patients, the impact would be insignificant, due to the low reported incidence (10%) of *c-KIT* mutations in association with trisomy 4 as the sole abnormality.²

This is the largest reported series of trisomy 4 in AML with extensive follow-up data. Evidence from this study confirms that these patients belong to the intermediate risk group, by comparison with patients with intermediate risk normal karyotype AML. The conclusion is that paediatric patients should be closely monitored for risk of relapse.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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