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Survival of Childhood Acute Lymphoid Leukaemia in Yorkshire by Clinical Trial Era, 1990-2011

Short Title: Survival of ALL by Clinical Trial

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Summary

Gender specific differences in survival by clinical trial era in Yorkshire were assessed for children with acute lymphoid leukaemia enrolled onto UKALLXI, ALL97/99 or UKALL2003 (n=630; 1990-2011). For males, there was a non-significant improvement in survival for ALL97/99 (hazard ratio (HR) = 0.77; 95%CI 0.43-1.42) and a significant improvement for UKALL2003 (HR=0.50; 95%CI 0.25-0.99) compared to UKALLXI. For females, survival was significantly improved for ALL97/99 (HR=0.33; 95%CI 0.14-0.78), and non-significantly improved for UKALL2003 (HR=0.51; 95%CI 0.25-1.08) compared to UKALLXI. Modest overall survival improvements masked clinically important gender-specific changes over time by trial era, requiring confirmation in larger population-based studies.

Keywords: acute lymphoid leukaemia, survival, clinical trial, paediatric

Introduction

Since the 1960s children with acute lymphoid leukaemia (ALL) have experienced improved 5 year overall survival rates from below 40% to 88% for those diagnosed between 2001-2005 (Stiller, 2007). These improvements have largely stemmed from effective chemotherapy administered through clinical trial protocols (Stiller et al, 2012). However, despite high accrual rates, the three most recently published MRC trials covering patients diagnosed since 1990 have shown fairly modest improvements in 5 year survival, with overall survival rates of 84.6%, 88.0% and 91.5% for UKALLXI (Hann et al, 2001), ALL97/99 (Mitchell et al, 2009) and UKALL2003 (Vora et al, 2013), respectively. Clinical observation in Yorkshire has noted gender-specific differences in survival and this study set out to investigate whether the survival chances of males differ from females for those with ALL entered onto clinical trials.

Materials and Methods

Cases of ALL diagnosed between 1st October 1990 and 30th June 2011 under the age of 15 were identified from the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP), a high quality population-based register. A range of ascertainment validation procedures were carried out to ensure optimal completeness (van Laar et al, 2010), including cross-checks with national clinical trials (Feltbower et al, 2009) and the regional Haematological Malignancy Research Network (www.hmrn.org/about/info). All new diagnoses are followed-up every year through flagging with the Office for National Statistics. Diagnoses were coded according to ICD-O-3 and classified according to the International Classification of Childhood Cancer, Third Edition (ICCC-3) which defines ALL (group Ia) as a distinct sub-group of leukaemia including the following tumours: B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma, Burkitt cell leukaemia, prolymphocytic leukaemia (B-cell, T-cell and NOS), precursor lymphocytic leukaemia (B-cell, T-cell and NOS), and lymphocytic leukaemia NOS (Steliarova-Foucher et al, 2005).

There were three main clinical trials for childhood ALL during the study period:

- UKALLXI, Oct 1990 - March 1997 (Hann et al, 2001)
- ALL97/99, April 1997- September 2003 (Mitchell et al, 2009; Mitchell et al, 2005; Vora et al, 2006)
- UKALL2003, Oct 2003 - June 2011 (Vora et al, 2013)

Overall survival (OS) for ALL was initially summarised by trial era using univariable Kaplan-Meier analysis. Missing data for white cell count (4.29%) and ethnicity (13.9%) was imputed using multiple imputation by chained equations (40 imputations), followed by a pooled multivariable Cox regression analysis over all imputation sets adjusting for trial era, age at diagnosis, sex, white cell count, Townsend deprivation score and ethnicity (south Asian and non-south Asian classified using name analysis and linked hospital episode statistic data, van Laar et al (2010) and (van Laar et al, 2014). Hazard ratios (HR) were used to summarise the relative difference in risk of death between covariates. Age was included in the model as a continuous variable, as there was no evidence of improved model fit by including a categorical age variable reflecting the morphological and prognostic features of ALL (0-1, 2-5, 6-14 years). Additionally, a sensitivity analysis was performed by removing those diagnosed under the age of 1, and comparing results to the model including all ages. Interactions between trial era and gender were also tested to determine whether the change in survival over time differed between males and females. The proportional hazards assumption was checked for each variable using the Therneau and Grambsch test within Stata, and showed that this assumption was met for all variables ($P>0.05$).

Results

There were a total of 630 diagnoses of ALL amongst children under the age of 15 in Yorkshire between 1990 and 2011. Table 1 shows the number of cases diagnosed within each trial period and the number who were known to be enrolled on each trial.

5-year OS estimates for those enrolled on UKALLXI, ALL97/99 and UKALL2003 trials were 83% (95% CI 76-88), 87% (95% CI 81-91) and 88% (95% CI 83-92) respectively, which compared to 5-year survival estimates of 60% (95% CI 42-75) for those enrolled on other trials, 74% (95% CI 55-86) for those not enrolled on a trial and 78% (95% CI 36-94) for those with missing trial data. We observed a significant difference between Kaplan-Meier survival curves for those enrolled onto the UKALLXI, ALL97/99 and UKALL2003 trials, with lowest survival estimates seen for the earliest trial ($P = 0.0185$). A borderline significant difference in Kaplan-Meier survival curves was observed by trial and gender in the univariable analysis (log-rank test $P = 0.0565$, Fig 1). Five-year survival by trial and gender showed that estimates were similar for males and females on UKALLXI (85%; 95% CI 75-91 and 81%; 95% CI 69-89 respectively) and UKALL2003 (89%; 95% CI 82-94 and 87%; 95% CI 78-92 respectively), whereas males on ALL97/99 (83%; 95% CI 75-89) had poorer

survival compared to females on the same trial (92%; 95% CI 84-96) although this was not significant.

These differences were confirmed in the multivariable analysis (Fig 2; Supplementary Table 1) whereby males showed a non-significant reduced risk of death for ALL97/99 (HR=0.77; 95% CI 0.43-1.42) and a significant reduced risk for UKALL2003 (HR=0.50; 95% CI 0.25-0.99) respectively compared to UKALLXI (P-value for linear trend in survival = 0.002). For females survival showed a non-linear relationship over time: a significantly lower risk of death was seen for those enrolled on ALL97/99 (HR=0.33; 95% CI 0.14-0.78) in contrast to males, followed by a non-significant reduced risk of death for UKALL2003 (HR=0.51; 95% CI 0.25-1.08), compared to UKALLXI (P-value for linear trend in survival = 0.160) which, although non-significant, was comparable to males in terms of its effect size. Despite differences in the effect of ALL97/99 compared to UKALLXI on survival between males and females, the overall interaction between gender and trial era was not significant (P-value = 0.065).

Additionally, we observed a significant increased risk of death associated with the logarithm of white cell count of 32% (HR=1.32, 95% CI 1.15-1.51; Supplementary Table 1), however, there was no significant interaction between logarithm of white cell count and trial era (P-value = 0.559).

We observed an increased risk of death associated with age at diagnosis of 4% (HR=1.04, 95% CI 0.98-1.10) for every single year increase in age, however, this effect was not significant (P-value = 0.158). All parameter estimates remained the same when removing those diagnosed under the age of 1 (n=20; 3.2%) from the model and when including deprivation and ethnicity either separately or simultaneously in the same Cox model.

Conclusions

Five-year survival estimates improved only slightly for those entered onto the two latest protocols, ALL97/99 and UKALL2003, compared to UKALLXI with OS of 87% and 88% observed in the latter two periods (1997-2003, 2003-2011) compared to 83% for the earliest trial era (1990-1997). However, these modest survival changes over time by trial era masked some important gender differences. OS rates improved for males between the earliest and trial periods, whilst females improved noticeably between UKALLXI and ALL97/99 before regressing for those on UKALL2003. This was confirmed by multivariable regression

modelling adjusting for white cell count, age, deprivation and ethnicity, although the interaction between gender and trial era was borderline non-significant (p=0.07).

Certain aspects of the trial treatment regimens may explain these differences. For instance, ALL97/99 was modified during its initial phase due to a lack of improvement in survival compared to other international studies (Chessells et al, 2002), by incorporating initial stratification by age, white cell count and early response to therapy. There could have been a differential distribution in these factors by gender, although our multivariable regression analysis controlled for these effects. Nonetheless we did not have detailed cytogenetic information available to inform this process further. The design of the intensification phases also changed significantly in ALL97/99 compared to UKALLXI and ALL97, so that these were extended from 5 days up to 8 weeks leading to a higher prevalence of cytopenias in the earlier trials, which could differ by gender. There were also noted differences in the type of asparaginase used in ALL97/99 and UKALL2003 compared to previous trials, which may acted differentially according to gender. Finally a small number of high risk patients randomised to ALL97 moved to a non-randomised study, HR1 (Kinsey et al, 2002) and these were more likely to be male (Chessells et al, 1995). HR1 patients were not analysed as part of the national ALL97/99 results, and this may therefore have contributed to these findings.

Limitations

The work presented here is an analysis of those enrolled onto national clinical trials, but only includes patients diagnosed within Yorkshire. The patients enrolled onto trials have been randomised at a national level; however, the group selected here is not necessarily a representative sample of the country and may have differed in terms of their immunophenotype and cytogenetic risk profile. Nonetheless this region in the north of England is representative in terms of its socio-demographic profile compared to the rest of the UK (Feltbower et al, 2004) and we have no reason to believe why clinical trial accrual rates or recruitment and treatment procedures would be any different to other parts of the UK due to standardised protocols. Almost all children in Yorkshire with ALL are treated at the tertiary regional centre for paediatric haematology and oncology at Leeds Teaching Hospitals NHS Trust, one of the 19 UK paediatric Principal Treatment Centres, therefore benefitting from an environment within a large cancer centre with a long track record of clinical research involving randomised trials.

In summary, further detailed national work is needed which should focus on evaluating and highlighting gender differences when reporting the results of clinical trials for ALL in children and young adults.

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Competing interests: the authors have no competing interests.

Contribution of authors: SEK and RGF designed the research study, MvL and RGF analysed and interpreted the data, MvL, RGF and SEK drafted, critically reviewed and approved the final version of the paper.

References

Chessells J, Richards S, Bailey C, Lilleyman J, Eden O (1995) Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the MRC UKALL trials*. British Journal of Haematology **89**(2)**:** 364-372

Chessells JM, Harrison G, Richards SM, Gibson BE, Bailey CC, Hill FG, Hann IM (2002) Failure of a new protocol to improve treatment results in paediatric lymphoblastic leukaemia: lessons from the UK Medical Research Council trials UKALL X and UKALL XI. Br J Haematol **118**(2)**:** 445-455

Feltbower R, Lewis I, Picton S, Richards M, Glaser A, Kinsey S, McKinney P (2004) Diagnosing childhood cancer in primary care–a realistic expectation? Br J Cancer **90**(10)**:** 1882-1884

Feltbower RG, McNally RJQ, Kinsey SE, Lewis IJ, Picton SV, Proctor SJ, Richards M, Shenton G, Skinner R, Stark DP (2009) Epidemiology of leukaemia and lymphoma in children and young adults from the north of England, 1990–2002. Eur J Cancer **45**(3)**:** 420-427

Hann I, Vora A, Harrison G, Harrison C, Eden O, Hill F, Gibson B, Richards S (2001) Determinants of outcome after intensified therapy of childhood lymphoblastic leukaemia: results from Medical Research Council United Kingdom acute lymphoblastic leukaemia XI protocol. Br J Haematol **113**(1)**:** 103-114

Kinsey S, Mitchell C, Harrison G, Richards S (2002) Treatment of High Risk Leukaemia – Results of MRC Childhood Acute Lymphoblastic Leukaemia Study MRC HR-1. Blood (ASH Annual Meeting Abstracts) **100:** 768a

Mitchell C, Payne J, Wade R, Vora A, Kinsey S, Richards S, Eden T (2009) The impact of risk stratification by early bone-marrow response in childhood lymphoblastic leukaemia: results from the United Kingdom Medical Research Council trial ALL97 and ALL97/99. Br J Haematol **146**(4)**:** 424-436

Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TOB (2005) Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol **129**(6)**:** 734-745

Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P (2005) International Classification of Childhood Cancer, Third Edition. Cancer **103:** 1457-67

Stiller C (2007) Childhood Cancer in Britain: Incidence, Survival, Mortality. Oxford University Press

Stiller CA, Kroll ME, Pritchard-Jones K (2012) Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. Ann Oncol **23**(9)**:** 2464-2469

van Laar M, Feltbower R, Gale C, Bowen D, Oliver S, Glaser A (2014) Cardiovascular sequelae in long-term survivors of young peoples' cancer: a linked cohort study. Br J Cancer **110**(5)**:** 1338-1341

van Laar M, McKinney PA, Parslow RC, Glaser A, Kinsey SE, Lewis IJ, Picton SV, Richards M, Shenton G, Stark DP, Norman P, Feltbower RG (2010) Cancer incidence among the south Asian and non-south Asian population under 30 years of age in Yorkshire, UK. Br J Cancer **103:** 1448-1452

Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R, Rowntree C, Richards S (2013) Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. The Lancet Oncology **14**(3)**:** 199-209

Vora A, Mitchell CD, Lennard L, Eden T, Kinsey SE, Lilleyman J, Richards SM (2006) Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. Lancet **368**(9544)**:** 1339

Table 1: Number of cases of acute lymphoid leukaemia and percentage of total diagnoses within each trial period in Yorkshire, 1990-2011

Trial and Period	Number Enrolled		Number not Enrolled	Total Enrolled	Total Cases[e]	Missing[d]
	Specified Trial[a]	Other Trial[b]	Not on Trial[c]			
UKALLXI (Oct 90 – March 97)	142	23	2	165 (99%)	167	0
ALL97/99 (Apr 97 – Sep 03)	178	30	8	209 (96%)	216	1
UKALL2003 (Oct 03 – Jun 11)	209	7	21	216 (91%)	237	9

[a]Number enrolled on UKALLXI, ALL97/99 or UKALL2003 within each trial period respectively

[b]Number known to be enrolled on a trial, but not on UKALLXI, ALL97/99 or UKALL2003

[c]Number known to not be enrolled on a trial

[d]Number without any trial data

[e]Total cases diagnosed within the respective trial periods

Figure 1: Kaplan-Meier estimates comparing survival of childhood acute lymphoblastic leukaemia by trial and gender (P-value for difference in survival curves = 0.0565).

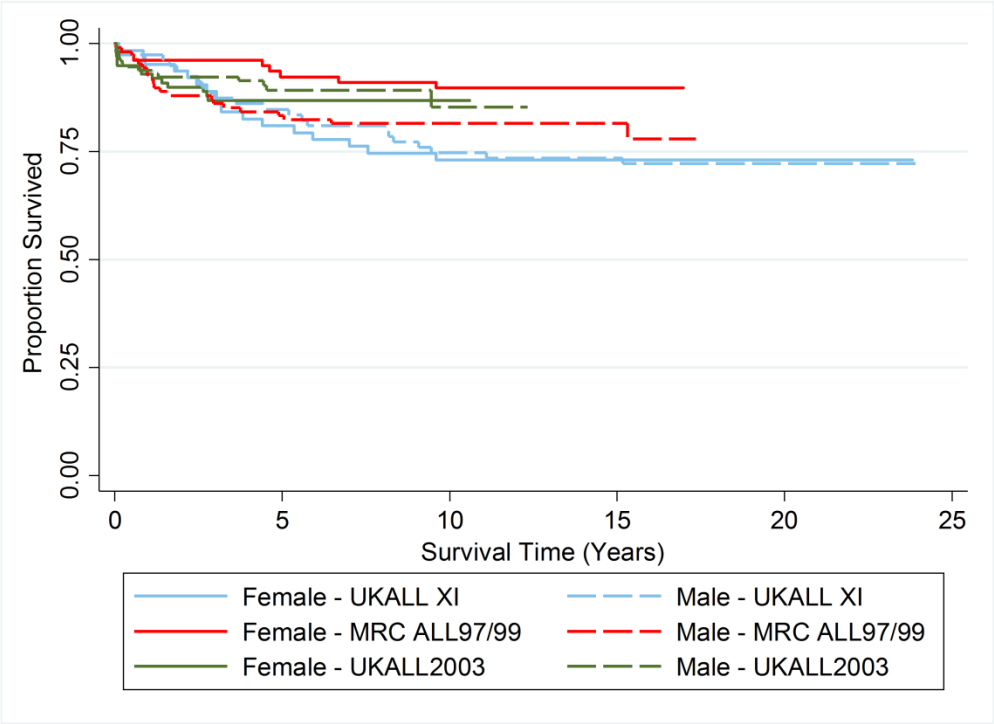
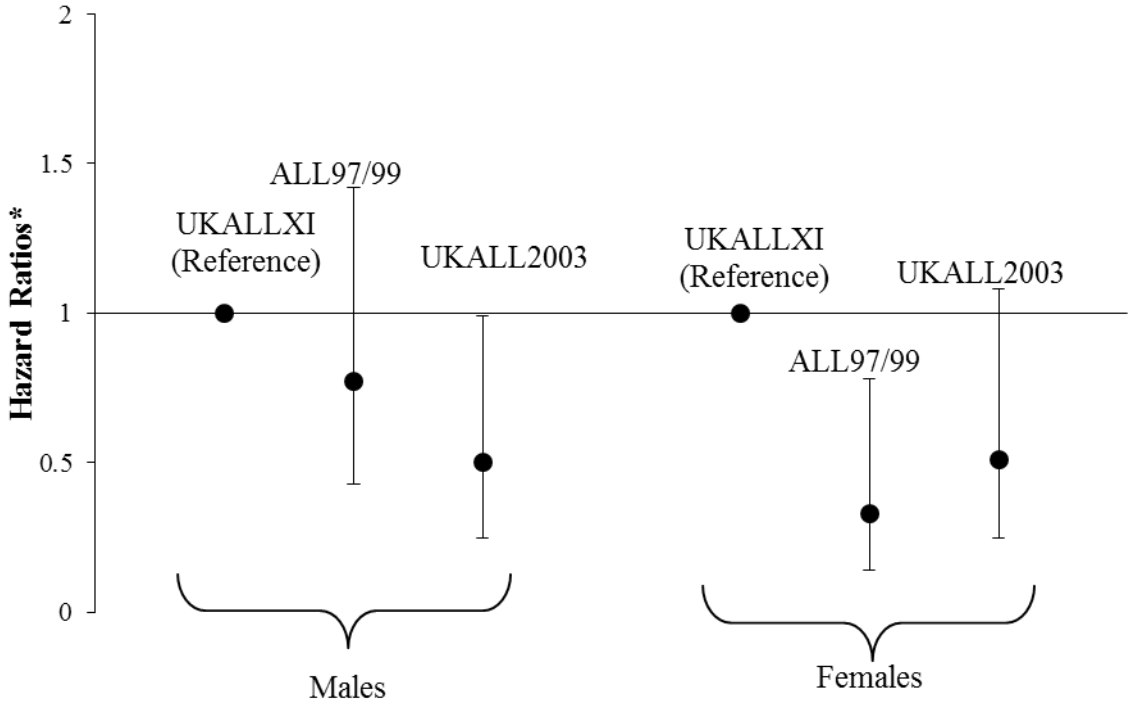


Figure 2: Hazard ratios and 95% confidence intervals obtained from a multivariable Cox regression model for survival of childhood ALL by clinical trial and gender in Yorkshire, 1990-2011 (Test for interaction P=0.065)



*Hazard ratios are adjusted for white cell count, age at diagnosis (in years), deprivation score and ethnicity (south Asian vs. non-south Asian)