BMJ Paediatrics Open

Osteonecrosis in patients with acute lymphoblastic leukaemia: a national questionnaire study

Nadia Laila Amin,[1,2] Richard Feltbower,[1] Sally Kinsey,[1,2] Ajay Vora,[3] Beki James[1]

To cite: Amin NL, Feltbower R, Kinsey S, *et al*. Osteonecrosis in patients with acute lymphoblastic leukaemia: a national questionnaire study. *BMJ Paediatrics Open* 2017;**1**:e000122. doi:10.1136/bmjpo-2017-000122

Received 30 May 2017
Revised 9 August 2017
Accepted 9 August 2017

ABSTRACT

Objectives To establish prevalence, management and long-term outcomes of osteonecrosis (ON) in young people diagnosed with acute lymphoblastic leukaemia (ALL) between 2003 and 2011.

Design, setting, participants This study assessed ON in 3113 patients aged 1–24 years who participated in the UK national leukaemia study UKALL 2003. UKALL 2003 recruited patients in 40 UK hospitals between 2003 and 2011 and included patients between ages 1 and 25 diagnosed with ALL.

Results 170 patients were diagnosed with ON, giving a prevalence of 5.5%. The multivariable analysis showed that the risk of ON was highest for children aged between 10 and 20 years (ages 10–15 years, OR 23.7, 95% CI 14.8 to 38.0; ages 16–20 years, OR 22.5, 95% CI 12.7 to 39.8, compared with age <10 years). Among ethnic groups, Asian patients had the highest risk of ON (OR 1.92, 95% CI 1.1 to 3.6, compared with White patients). Eighty-five per cent of patients with ON had multifocal ON. Thirty-eight per cent of patients with ON required surgery and 19% of patients with ON required a hip replacement. Fifteen per cent of patients who had surgery still describe significant disability or use of a wheelchair.

Conclusions ON has considerable morbidity for patients being treated for ALL, with a high burden of surgery. Age and ethnicity were found to be the most significant risk factors for development of ON, with Asian patients and patients aged 10–20 years at diagnosis of ALL at greatest risk. These results will help risk stratify patients at diagnosis of ALL, and help tailor future prospective studies in this area.

What is already known on this topic?

- Patients being treated for acute lymphoblastic leukaemia (ALL) are at increased risk of development of osteonecrosis (ON), which is likely to be an iatrogenic complication.
- Previous studies have found that patients aged over 10 years at diagnosis of ALL have increased risk of developing ON.

What this study hopes to add?

- This study has found a UK prevalence of symptomatic ON of 5.5%.
- Asian ethnicity is a significant risk factor for development of ON.
- Analysis highlights the burden of surgery in patients, with 38% of patients with ON requiring some form of surgery.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common type of children's leukaemia, accounting for 78% of all leukaemias diagnosed in paediatrics,[1] with 420 patients aged 24 years or younger newly diagnosed each year in the UK.[2]

As progressive intensification of chemotherapy continues to improve outcomes,[3 4] there has been an increasing focus on understanding and limiting the long-term complications of treatment for paediatric ALL. The challenge is to maintain excellent outcomes for patients with ALL while reducing disability.

Morbidity after ALL varies considerably with treatment received. Osteonecrosis (ON) is one of the most debilitating complications seen during or after treatment for ALL, and is mostly an iatrogenic complication that has been attributed to increased use of glucocorticoids.[5] Asparaginase,[6] high-dose methotrexate[7] and cyclophosphamide[8] have also been implicated; however, causation has not been established. Development of ON appears to be multifactorial, but is being reported more commonly in patients as survival improves and high-dose steroids have become embedded in treatment regimens.[9 10]

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events provides an internationally recognised definition of ON, and defines it as 'a disorder characterised by necrotic changes in the bone tissue due to interruption of blood supply'.[11] The Ponte di Legno toxicity working group developed a more clinically relevant consensus-based definition and grading system to enable reliable

[1]Paediatric haematology, Leeds Children's Hospital, Leeds, UK
[2]University of Leeds, Leeds, UK
[3]Paediatric haematology, Great Ormond Street Hospital, London, UK

Correspondence to
Dr Nadia Laila Amin; nadia@cantab.net

comparison of frequency and severity,[12] with ON defined as 'result[ing] from the temporary or permanent loss of the blood supply to the bones, which can cause pain, limitation in activity of daily living, and potentially the collapse of an articulating surface with enhanced pain and development of arthritis'.[12]

There is little published information on long-term outcomes for children and young people who develop ON subsequent to treatment for ALL, and as such this study is crucial in understanding the natural history and current management of ON in the UK.

The primary outcome measure of this study was to report the UK prevalence of symptomatic ON in young people with ALL. Secondary outcome measures included identification of risk factors for development of ON, timing of development of symptomatic ON, time taken to diagnose ON, joints affected by ON, surgical requirements and long-term outcomes in patients with ON.

METHODS

Study population

A total of 3207 patients aged 1–24 years were registered onto the UK ALL trial UKALL 2003, of whom 3113 were eligible for analysis, and were included in this study. Reasons for exclusion from analysis included 70 patients who were Philadelphia chromosome positive, 14 patients who were misdiagnosed, 7 patients who withdrew consent and 3 patients who were registered twice. Philadelphia chromosome-positive patients were excluded as they were treated on alternative treatment protocols once Philadelphia chromosome status was established.

Patients were recruited into UKALL 2003 in 40 UK hospitals between 2003 and 2011.[13] All patients had a diagnosis of ALL, which was diagnosed with standard morphological and flow cytometric criteria.[14] Patients were categorised into standard, intermediate and high-risk groups based on a combination of NCI criteria, cytogenetics and early response to induction therapy, assessed by bone marrow blast counts. Standard and intermediate-risk patients were assessed for minimal residual disease (MRD), and those classified as MRD low risk were randomly assigned to receive one or two courses of delayed intensification. Full details of treatment have been previously described.[13] All patients received a daily dose of 6 mg/m^2 oral dexamethasone during induction and maintenance, with a maximum dose of 10 mg. In delayed intensification, all patients received 10 mg/m^2 dexamethasone daily for 2 weeks, on alternate weeks, with no cap on dose.

Identification of patients with ON

Patients with reported bone toxicity were initially identified by the Clinical Trials Service Unit (CTSU) for UKALL 2003, through return of toxicity reporting or serious adverse event (SAE) forms. Toxicity reporting forms specifically requested data regarding ON, where it was categorised as unacceptable bone toxicity (NCI grade 4). A SAE was defined as any adverse event that resulted in death, was life threatening, required unexpected hospitalisation or unexpected prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity.

The treatment centre for each patient was contacted and provided with a list of all patients identified at that centre. A questionnaire was provided for each patient and information was also requested for any additional UKALL 2003 patients known to the centre as having ON.

Questionnaires and identified patient lists were distributed for completion by clinicians and research nurses in each treatment centre, who were contacted between 8 April 2015 and 20 April 2015.

All diagnoses of ON were confirmed by assessment of radiological reports produced by local radiologists. Long-term effects were defined as the effect of ON on the patient at the most recent follow-up consultation.

Statistical analysis was undertaken using univariable and multivariable logistic regression analyses to identify significant differences in the prevalence of ON according to age group at diagnosis (ages <10, 10–15 and 16+ years), sex, ethnicity (white, black, Asian, other) and treatment (one or two rounds of delayed intensification). Ethnicity was assigned based on self-report and categories defined in each centre. These variables were selected due to results of previous studies which suggested their possibility of association with development of ON. ORs and 95% CIs were reported as measures of association. All analyses were carried out using Stata V.14 (StataCorp, 2015).

RESULTS

There was a 90% questionnaire response rate between 9 April 2015 and 12 December 2015 for the 292 eligible patients with bone toxicity identified by the CTSU. Of these patients, 170 had radiographically confirmed ON, giving a prevalence of ON of 5.5% (170/3113) (figure 1). Alternative conditions recorded as bone toxicity included diagnoses such as fractures, osteopenia and osteoporosis, but details of alternative diagnoses and imaging were not collated. Median duration of follow-up for patients from time of ALL diagnosis was 70.5 months (range 24–127 months, IQR 54–86 months).

No explanation was given for the lack of questionnaire completion in 26 of the 29 non-responders, and notes were not available for three of the patients. Demographic details of these 29 patients are provided in table 1. These patients were not included in our overall analysis of patients, as ON was not able to be confirmed.

Timing

The median time for development of symptoms of ON after diagnosis of ALL or lymphoblastic lymphoma was 14 months (IQR 10–19 months). The median time to diagnosis of ON was 16 months (IQR 12–22 months) after the initial diagnosis of ALL. Date of diagnosis of ON was not available for six patients. Of the remaining

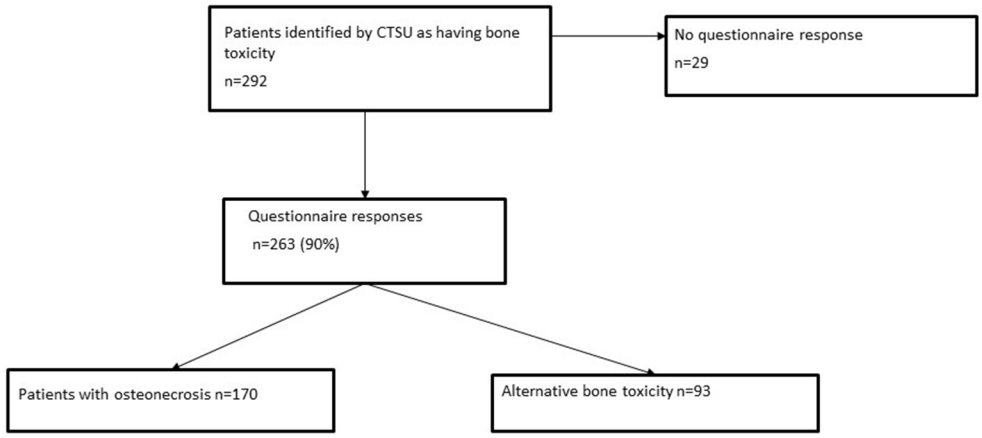

Figure 1 Questionnaire response flow chart. CTSU, Clinical Trials Service Unit.

164 patients, 35 were diagnosed with ON in the first year after diagnosis of malignancy (21% of all patients diagnosed with ON), 91 were diagnosed during the second year (55%) and 25 were diagnosed during the third year (15%). Eight patients were diagnosed between 3 and 5 years after diagnosis of malignancy, and only two patients were diagnosed with ON after 5 years. The last diagnosis of ON was made at 6.26 years after diagnosis of ALL. As such, the cumulative incidence of ON diagnosed in all patients with ALL was 1.1% at 1 year, 4.0% at 2 years, 4.9% after 3 years, 5.1% at 5 years and 5.2% at 7 years. For patients over the age of 10 at diagnosis of ALL, the cumulative incidence of ON was 3.3% at 1 year, 12.5% at 2 years, 15.1% at 3 years, 16% at 5 years and 16.2% at 7 years.

Risk factors

Age, ethnicity, gender and one versus two delayed intensification blocks were assessed in terms of their univariable and multivariable association with the risk of ON (table 2).

It can be seen that age at diagnosis of ALL was found to be a significant risk factor for development of ON. All age groups above the age of 10 were at significantly higher risk for development of ON, although the highest OR (23.73) was for those aged between 10 and 15 years compared with those less than 10 years of age. The OR reduced to 8.32 for those aged over 20 at diagnosis of ALL. Figure 2 illustrates the ages of all patients who developed ON.

On multivariable regression analysis Asian ethnicity was also found to be independently associated with the development of ON, with an OR of 1.92 (95% CI 1.05 to 3.55).

Joints affected

The majority of patients had multifocal ON, with a total of 480 joints affected in the 170 patients. Only 15% of patients (n=26) had unifocal ON. The most commonly affected joints were hips (34%), knees (32%), shoulders (14%) and ankles (10%). In the patients under the age of 10 years at diagnosis of ALL, 21% had unifocal ON.

Table 1 Demographic details for trial patients and patients with missing data

	Patients with confirmed osteonecrosis (%)	Patients with no questionnaire response (%)	All trial patients
Age (years) at diagnosis of ALL			
<10	22 (1.0)	3 (0.1)	2279
10–15	111 (18.3)	10 (1.6)	607
16+	35 (15.4)	16 (7.0)	227
Ethnicity			
White	141 (5.6)	25 (1.0)	2525
Asian	15 (6.5)	2 (0.9)	74
Black	3 (4.0)	1 (1.3)	232
Other	11 (7.2)	1 (0.7)	164
Unknown/missing	0	0	118
Gender			
Male	96 (5.4)	19 (1.1)	1767
Female	74 (5.5)	10 (0.7)	1346

ALL, acute lymphoblastic leukaemia.

Table 2 Results of univariable and multivariable logistic regression analyses for variables associated with osteonecrosis

			Univariable logistic regression			Multivariable logistic regression		
	With osteonecrosis (frequency (%))	Without osteonecrosis (frequency (%))	OR	CI	p Value	OR	CI	p Value
Age (years)								
<10	22 (1)	2257 (99)				1.00		
10–15	111 (18)	496 (82)	22.96	14.38 to 36.64	<0.001	23.73	14.82 to 38.00	<0.001
16–20	32 (17)	154 (83)	21.31	12.09 to 37.57	<0.001	22.45	12.66 to 39.81	<0.001
21+	3 (7)	38 (93)	8.10	2.32 to 28.22	0.001	8.32	2.38 to 29.12	0.001
Ethnicity								
White	141 (6)	2384 (94)				1.00		
Black	3 (4)	71 (96)	0.73	0.23 to 2.35	0.60	0.94	0.27 to 3.23	0.92
Asian	15 (6)	217 (94)	1.20	0.69 to 2.07	0.53	1.92	1.05 to 3.55	0.04
Other/ unknown	11 (4)	271 (96)	0.91	0.52 to 1.59	0.73	0.99	0.52 to 1.88	0.99
Gender								
Male	96 (5)	1671 (95)				0.91	0.65 to 1.28	0.59
Female	74 (5)	1272 (95)	1.04	0.76 to 1.43	0.79	1.00		
Number of delayed intensifications								
2	138 (6)	2142 (94)				1.00		
1	31 (4)	802 (96)	0.85	0.59 to 1.22	0.38	0.99	0.67 to 1.45	0.94

Surgical requirements

Surgery was reported in 65 of the 170 patients (38%), with 99 surgical procedures reported in these patients. Table 3 shows the types of surgery performed. Hip replacements were the most common form of surgery required, with 19% of patients affected.

Of the patients for whom arthroscopy was performed, three received arthroscopy alone. Additional procedures done alongside arthroscopy included synovial debridement, meniscotomy, correction of osteochondral defects, reshaping of femoral head, core decompression, removal of loose bodies and joint stabilisation.

Sixteen patients (9%) had more than one joint to be replaced as a result of ON. Twelve patients had bilateral hip replacements, one patient needed bilateral hip replacements and a knee replacement, two needed a shoulder and hip replacement, and one had a knee and hip replaced.

Of the patients who were under the age of 10 at diagnosis of ALL, only four had ON which had any surgical

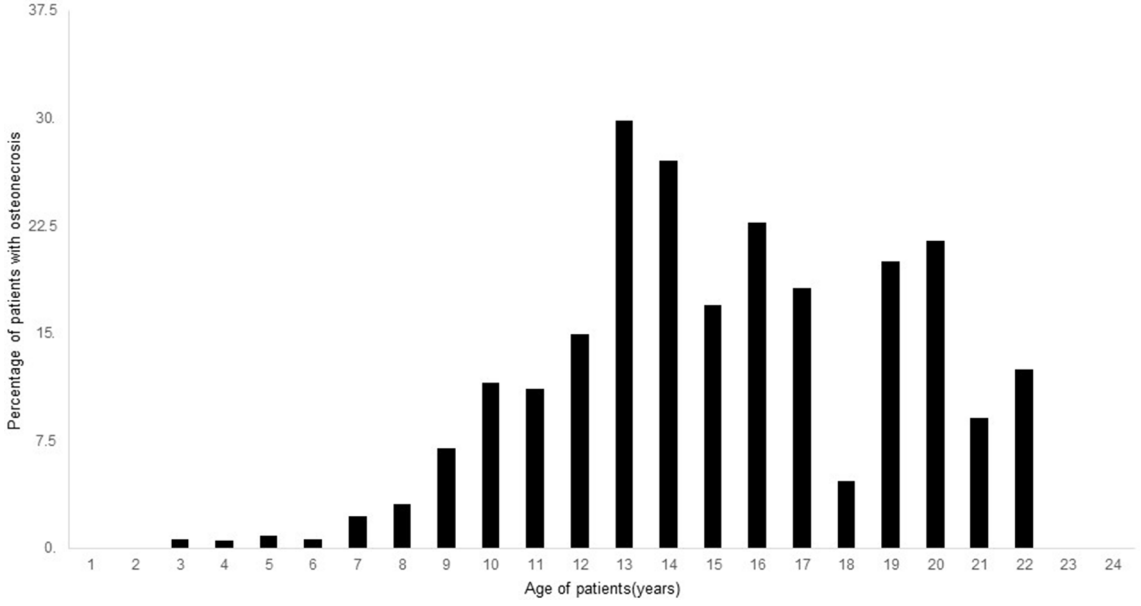

Figure 2 Age of all patients with osteonecrosis.

Table 3 Surgical procedures in patients with ON

Type of surgery	Number of patients	Percentage of patients with ON affected
Hip replacement	33	19
Core decompression	22	13
Knee replacement	2	1
Shoulder replacement	2	1
Arthroscopy	10	6
Hip fixation	2	1
Other	10	6

ON, osteonecrosis.

management. Two of these patients needed joint replacements, with the other two receiving core decompression. These patients were aged between 6 and 8 at diagnosis of ALL.

Despite the high surgical requirement in patients with ON, at time of data collection the majority of patients who had ON were reported to have either no long-term effects (39%, n=66) or minimal disability (38%, n=64). Nine per cent of patients continued to have significant disability (n=16) and five patients required a wheelchair (3%). Six per cent of patients had died and information was not available for nine other patients (5%). This distribution was similar for patients both over and under 10 years at diagnosis of ALL.

Of the patients who had surgery, 54% (n=35) were reported to have minimal disability and 29% reported no long-term effects. Despite surgical intervention, seven patients (11%) still described the presence of significant disability and three patients required a wheelchair at the time of data collection.

DISCUSSION

This is the largest study reporting symptomatic ON in childhood ALL, providing long-term follow-up data of patients. The prevalence of ON in our population was 5.5%, and as with previous studies, age was the most important risk factor for development of ON.[10 15–18] This study found 18% and 17% of patients between 10 and 15 years and 16 and 20 years, respectively, develop ON, compared with only 1% of patients aged less than 10 years. It is also noteworthy that there was a significant reduction in percentage of patients who developed ON if they were diagnosed with ALL after the age of 20, with only 7% of this group of patients developing ON. Our study is also the first study to describe an increased risk of ON in Asian patients after adjustment for age, gender and treatment.

Hips, knees, shoulders and ankle joints were most commonly affected by ON, and one of the most remarkable findings was the huge burden of surgery in this patient population. Hip replacement was required by 19% of patients affected by ON, and of all patients over 10 years of age at diagnosis of ALL, 3.6% required at least one joint to be replaced.

Strengths of this work include the large sample size, national data set, high response rate and long follow-up period.

Limitations include the retrospective nature of the study, collecting data from patients from UKALL 2003, who were diagnosed with ALL between 1 October 2003 and 30 August 2011. This may have resulted in recall bias, with more severe forms of ON recorded or recalled, which could enrich our data with a higher percentage of adverse outcomes, such as surgical requirements. Asymptomatic ON was not detected, and there was no specified threshold for imaging of patients or criteria for joint imaging. We were also unable to centrally review the MRI images, relying on local reports to determine the diagnosis of ON. This study did not incorporate grading and severity of ON due to variability in MRI reporting across centres. As treatment decisions for each patient were made individually, and data on ON severity are not available, comparability and generalisability of data on management and long-term outcome are limited. The reader should also be aware that the patients were treated on a specific ALL protocol, outlined previously, and the demography of our patients may differ from those in other geographical locations.

The prevalence of ON in the literature is strikingly variable from 0.43% to 26.6%.[15 19] This variation is likely to be due to a number of factors, including study design, method of diagnosis of ON and reporting methods. The majority of studies also reported only symptomatic ON, with much higher rates reported in studies prospectively assessing asymptomatic ON.[20]

In our study, sex of the patient was not found to be a significant risk factor for development of ON. Previous studies have found conflicting results. A number of studies have found female sex to be a risk factor,[10 16 18 21–25] while many others found no such association,[17 26–33] even when similar treatment regimens were used.[10 17] Even in groups with the highest reported rates of ON there were disparate results—a Children's Cancer Group study reported the disorder more frequently in women,[18] while no gender differences were found in the Dana-Farber Cancer Institute consortium[31] and studies at St Jude Children's Research Hospital.[30]

This study describes the increased prevalence of ON in patients of Asian origin. Categorisation of ethnicity poses many difficulties,[34] as ethnic identification is often subjective,[35] and in this study the method of determining ethnicity was not clearly defined. There is also likely to have inconsistency between ethnic classifications among different countries, particularly with the term 'Asian', which in the UK is typically used for people who describe themselves as South Asian. Studies based in the USA typically used the term Asian for those of East Asian origin (Han Chinese and Japanese ancestries), in whom there was found to be no increased risk of ON.[16] There are clear reasons why there may be a difference between ethnic groups due to

genetic predispositions to obesity, diabetes, variation in bone mineralisation and handling of steroids, but more needs to be understood about the pathophysiology of ON development. In previous studies, white race was found to be a risk factor for development of ON,[16 18 19] but this is not consistently replicated.[20 32] In the majority of studies, method of assigning ethnicity was typically not discussed, and the racial groupings used varied. A number of studies separated patients into white and non-white, while others included black and Hispanic ethnic groups. No other studies specifically commented on South Asian patients, and most studies where race was commented upon were composed of predominantly white patients.

The median time for development of symptoms of ON after diagnosis of ALL was 14 months. We found that the number of courses of delayed intensification had no impact on the development of ON, despite the increased dexamethasone received by patients who received two courses of delayed intensification. This suggests the initial insult occurs early in the treatment course, with symptoms occurring later. This is supported by the largest prospective study to date looking at symptomatic and asymptomatic ON, where 364 patients with newly diagnosed ALL had MRI of the hips and knees after the completion of reinduction I (weeks 7–9) and reinduction II (weeks 17–19), and at the completion of therapy.[20] At the first MRI screen, 141 patients were found to have asymptomatic ON and 8 patients were found to have symptomatic ON. Patients who initially had asymptomatic ON were more likely to develop symptomatic ON (26%), compared with patients who were initially negative for ON (14%).

The need for a well-designed prospective study looking at ON in young people in the UK with ALL is clear, as the natural history of ON in the paediatric population and factors predicting long-term outcome are not well defined. It is possible that early intervention, prior to development of symptoms of ON, would improve joint outcome.

Acknowledgements The authors thank all the consultants, research nurses anddata managers at the following hospitals who provided us with patientinformation: Addenbrooke's NHS Trust, Alder Hey Children's Hospital, BirminghamChildren's Hospital, Bristol Royal Hospital for Children, Christie HospitalsNHS Trust, Clatterbridge Centre for Oncology, Great Ormond Street Hospital forChildren NHS Trust, Guy's Hospital, Leeds General Infirmary, Leicester RoyalInfirmary, Northampton General Hospital, Nottingham University Hospital, OurLady's Hospital for Sick Children, Oxford Radcliffe Hospitals, Royal AberdeenChildren's Hospital, Royal Belfast Hospital, Royal Hallamshire Hospital, RoyalHospital for Sick Children, Royal Manchester Childrens Hospital, Royal MarsdenHospital, Royal Victoria Infirmary, Sheffield Children's Hospital, SouthamptonUniversity Hospital Trust, Taunton and Somerset NHS Trust, University CollegeHospital, University Hospital of North Staffordshire, University Hospital ofWales, Western General Hospital, Yorkhill NHS Trust. We would also like to thank Nick Goulden, Rachel Wade,Chris Mitchell, Jeremy Hancock, Rachel Hough, Clare Rowntree and Sue Richardsfor their work on the original UKALL2003 study. The authors also acknowledge Alison Franklin for her helpwith the questionnaire design and distribution, Rachel Clack at the centraltrial unit for her help with data acquisition, and Professor Moorman for his assistancewith data acquisition.

Contributors NLA designed the data collection tools, developed the methodology, acquired, analysed and interpreted the data, and wrote and revised the manuscript. She is the guarantor. BJ designed the data collection tools, developed the methodology, and wrote and revised the manuscript. RF analysed and interpreted the data, and wrote and revised the manuscript.SK developed the data collection tools, and wrote and revised the manuscript. AV wrote and revised the manuscript. Study supervision was by BJ, SK and RF.

Competing interests None declared.

Ethics approval Scottish Multi-Centre Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The relevant anonymised patient-level data are available on reasonable request from the authors.

REFERENCES

1. Childhood cancer research group. *Children's cancers incidence statistics*. UK: Cancer research. http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/incidence#heading-Three1996-2005.
2. NCIN. Progress report: National registry of childhood tumours. 2012.
3. Public health england. Trends in incidence and outcome for haematological cancers in England: 2001-2010. 2014 http://www.ncin.org.uk/view?rid=2818 (accessed 23 Dec 2016).
4. Hunger SP, Lu X, Devidas M, *et al*. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* 2012;30:1663–9.
5. Barrack RL. Symptomatic multifocal osteonecrosis: a multicenter study. *Clinical orthopaedics and related research* 1999;369:312–26.
6. Hanada T, Horigome Y, Inudoh M, *et al*. Osteonecrosis of vertebrae in a child with acute lymphocytic leukaemia during L-asparaginase therapy. *Eur J Pediatr* 1989;149:162–3.
7. Kardos G, Ronde F, Bourier M, *et al*. Avascular necrosis of bone in children with acute lymphoblastic leukemia. *Med Pediatr Oncol* 1995;25:286.
8. Ishii E, Yoshida N, Miyazaki S. Avascular necrosis of bone in neuroblastoma treated with combination chemotherapy. *Eur J Pediatr* 1984;143:152–3.
9. Mattano LA, Nachman JB, Devidas M, *et al*. Increased Incidence of Osteonecrosis (ON) with a Dexamethasone (DEX) Induction for High Risk Acute Lymphoblastic Leukemia (HR-ALL): a report from the Children's Oncology Group (COG). American society of haematology 2008.
10. Aricò M, Boccalatte MF, Silvestri D, *et al*. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. *Haematologica* 2003;88:747–53.
11. US department of health and human services. Common terminology criteria for adverse events.2009:4 http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
12. Schmiegelow K, Attarbaschi A, Barzilai S, *et al*. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. *Lancet Oncol* 2016;17:e231–e239.
13. Vora A, Goulden N, Wade R, *et al*. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. *Lancet Oncol* 2013;14:199–209.
14. Szczepański T, van der Velden VH, van Dongen JJ. Classification systems for acute and chronic leukaemias. *Best Pract Res Clin Haematol* 2003;16:561–82.
15. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, *et al*. Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2008;26:3038–45.
16. Karol SE, Yang W, Van Driest SL, *et al*. Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia. *Blood*2015;126:1770–6. blood-2015-2005-643601.
17. Bürger B, Beier R, Zimmermann M, *et al*. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)-experiences from trial ALL-BFM 95. *Pediatr Blood Cancer* 2005;44:220–5.

18. Mattano LA, Sather HN, Trigg ME, *et al*. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the children's cancer group. *J Clin Oncol* 2000;18:3262–72.
19. Relling MV, Yang W, Das S, *et al*. Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. *J Clin Oncol* 2004;22:3930–6.
20. Kawedia JD, Kaste SC, Pei D, *et al*. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. *Blood* 2011;117:2340–7.
21. Mattano LA, Devidas M, Nachman JB, *et al*. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. *Lancet Oncol* 2012;13:906–15.
22. French D, Hamilton LH, Mattano LA, *et al*. A PAI-1 (SERPINE1) polymorphism predicts osteonecrosis in children with acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2008;111:4496–9.
23. Mitchell CD, Richards SM, Kinsey SE, *et al*. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol* 2005;129:734–45.
24. te Winkel ML, Pieters R, Hop WC, *et al*. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J Clin Oncol* 2011;29:4143–50. JCO. 2011.2037. 3217.
25. Niinimäki RA, Harila-Saari AH, Jartti AE, *et al*. High body mass index increases the risk for osteonecrosis in children with acute lymphoblastic leukemia. *J Clin Oncol* 2007;25:1498–504.
26. Patel B, Richards SM, Rowe JM, *et al*. High incidence of avascular necrosis in adolescents with acute lymphoblastic leukaemia: a UKALL XII analysis. *Leukemia* 2008;22:308–12.
27. Salem KH, Brockert AK, Mertens R, *et al*. Avascular necrosis after chemotherapy for haematological malignancy in childhood. *Bone Joint J* 2013;95-B:1708–13.
28. Elmantaser M, Stewart G, Young D, *et al*. Skeletal morbidity in children receiving chemotherapy for acute lymphoblastic leukaemia. *Arch Dis Child* 2010;95:805–9.
29. Relling MV, Boyett JM, Blanco JG, *et al*. Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. *Blood* 2003;101:3862–7.
30. Ribeiro RC, Fletcher BD, Kennedy W, *et al*. Magnetic resonance imaging detection of avascular necrosis of the bone in children receiving intensive prednisone therapy for acute lymphoblastic leukemia or non-Hodgkin lymphoma. *Leukemia* 2001;15:891–7.
31. Strauss AJ, Su JT, Dalton VM, *et al*. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol* 2001;19:3066–72.
32. Kaste SC, Pei D, Cheng C, *et al*. Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids. *J Clin Oncol* 2015;33:610–5. 2057. 5480.
33. Badhiwala JH, Nayiager T, Athale UH. The development of thromboembolism may increase the risk of osteonecrosis in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2015;62:1851–4.
34. Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. *BMJ* 1994;309:327–30.
35. Office For National Statistics. *Ethnic group statistics: a guide for the collection and classification of ethnicity data*: Office For national statistics, 2003.