PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The British OsteoNEcrosis Study (BONES) protocol: A prospective cohort study to examine the natural history of osteonecrosis in older children, teenagers and young adults with acute lymphoblastic leukaemia and lymphoblastic lymphoma
AUTHORS	Amin, Nadia; Kinsey, Sally; Feltbower, Richard; Kraft, Jeannette; Whitehead, Elizabeth; Velangi, Mark; James, Beki

VERSION 1 - REVIEW

REVIEWER	Dr Bhavna Padhye The children's Hospital at Westmead , Sydney, Australia
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	It is a well written protocol, easy to read and follow in general oncology clinic. When completed it will add significantly to our current understanding of osteonecrosis as we lack prospective data on this complication (as most studies are retrospective)

REVIEWER	Riitta Niinimäki Consultant Paediatric Haematologist and oncologist Oulu University Hospital Finland
REVIEW RETURNED	21-Dec-2018

GENERAL COMMENTS	This current study protocol explores the incidence and risk factors of symptomatic and asymptomatic osteonecrosis in the lower extremities in survivors of ALL and LBL diagnosed aged 10-24 years. One of the aims is to find out the specific radiological features that predict for either progression or regression in those with asymptomatic osteonecrosis. The study is well planned. Minor comments: Abstract According to earlier studies it is known that osteonecrosis in cancer patients can be located all over the skeleton, not just lower extremities but also for upper extremities. The location of ON should be added: "the main aim is to determine the incidence of symptomatic and asymptomatic osteonecrosis in lower

	extremities..." Also, it should be added to the limitations that only osteonecrosis of lower extremities will be examined. Introduction Age as a risk factor has been described well with appropriate references. Other risk factors (sex and ethnicity) have been mentioned without references. High BMI has not been mentioned. Please, revise the clinical risk factors and add the references. The chapter describing radiological classification is without references. Please, specify the classifications and add references. Methods and analysis MRI imaging Please describe how osteonecrosis is defined radiologically. Data analysis plan "The grade of osteonecrosis will be assessed using a modified scoring system by reference using a study radiology proforma". Please add reference or explain more specifically. Could you specify, if patient will develop symptomatic ON in upper limb, how the patient will be managed if she or he did not have any lesions in the lower limbs? Pain score is including also upper limbs.

REVIEWER	Archie Bleyer Oregon Health & Science University McGovern Medical School, University of Texas
REVIEW RETURNED	06-Jan-2019

GENERAL COMMENTS	This is a very important study that in general is ready to be started. Several problems need to be addressed beforehand, however. <p> 1. The statistical analysis is not presented, with the entire statistical section a single line that describes where it the statistical analysis will be done. Before a study of this type should be initiated, the feasibility, number of patients required (power), data validity/veracity, etc. must be proactively considered. <p> 2. Many germane prior publications are not discussed or even cited: <p> Hough R. Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003 Multicenter Study; Randomized Controlled Trial. Br J Haematol. 2016. doi: 10.1111/bjh.13847 <p> Nadia Amin, Sally Kinsey, Richard Feltbower, Ajay J. Vora, Nicholas Goulden, Rachel Wade, Chris Mitchell, Rachael Hough, Clare Rowntree, Beki James. Osteonecrosis in UKALL 2003: Blood 2015 126:2083 <p> Karol SE, Yang W, Van Driest SL, Chang TY, Kaste S, Bowton E, Basford M, Bastarache L, Roden DM, Denny JC, Larsen E, Winick N, Carroll WL, Cheng C, Pei D, Fernandez CA, Liu C, Smith C, Loh ML, Raetz EA, Hunger SP, Scheet P, Jeha S, Pui CH, Evans

WE, Devidas M, Mattano LA Jr, Relling MV. Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia. Blood. 2015 Oct 8;126(15):1770-6
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Liu C, Janke LJ, Kawedia JD, Ramsey LB, Cai X, Mattano LA Jr, Boyd KL, Funk AJ, Relling MV. Asparaginase Potentiates Glucocorticoid-Induced Osteonecrosis in a Mouse Model. PLoS One. 2016 Mar 11;11(3):e0151433. doi: 10.1371/journal.pone.0151433
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Kunstreich M, Kummer S, Laws HJ, Borkhardt A, Kuhlen M. Osteonecrosis in children with acute lymphoblastic leukemia. Haematologica. 2016 Nov;101(11):1295-1305.
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Mogensen SS, Schmiegelow K, Grell K, Albertsen BK, Wehner PS, Kampmann P, Frandsen TL. Hyperlipidemia is a risk factor for osteonecrosis in children and young adults with acute lymphoblastic leukemia. Haematologica. 2017 May;102(5):e175-e178. doi: 10.3324/haematol.2016.160507.
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Riccio I, Pota E, Marcarelli M, Affinita MC, Di Pinto D, Indolfi C, Del Regno N, Esposito M. Osteonecrosis as a complication in pediatric patients with acute lymphoblastic leukemia. Pediatr Med Chir. 2016 Nov 28;38(3):118. doi: 10.4081/pmc.2016.118.
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den Hoed MA, Pluijm SM, Uitterlinden AG, Pieters R, van den Heuvel-Eibrink MM. Genetic Biomarkers to Identify the Risk of Osteonecrosis in Children with Acute Lymphoblastic Leukemia. Mol Diagn Ther. 2016 Dec;20(6):519-522.
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Padhye B, Dalla-Pozza L, Little D, Munns C. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). Cancer Med. 2016 May;5(5):960-7. doi: 10.1002/cam4.645.
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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 Oct;62(10):1851-4
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Hyakuna N, Shimomura Y, Watanabe A, Taga T, Kikuta A, Matsushita T, Kogawa K, Kawakami C, Horikoshi Y, Iwai T, Okamoto Y, Tsurusawa M, Asami K; Japanese Childhood Cancer and Leukemia Study Group (JCCLSG). Assessment of corticosteroid-induced osteonecrosis in children undergoing chemotherapy for acute lymphoblastic leukemia: a report from the Japanese Childhood Cancer and Leukemia Study Group. J Pediatr Hematol Oncol. 2014 Jan;36(1):22-9. doi: 10.1097/MPH.0000000000000039.
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Krull K, Kunstreich M, Klasen-Sansone J, Kloetgen A, Gruener F, Escherich G, Bleckmann K, Moericke A, Schrappe M, Jorch N, Steinbach D, Classen CF, Guggemos A, Kolb R, Klee D, Borkhardt A, Kuhlen M. Osteonecrosis develops independently from radiological leukemic infiltration of bone in adolescents with acute lymphoblastic leukemia - first findings of the OPAL trial. Leuk Lymphoma. 2017 Oct;58(10):2363-2369. doi: 10.1080/10428194.2017.1280605.
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	As a result, some of the planning is incomplete relative to the state of the science/art. <p> 3. There are 3 types of avascular necrosis (AVN) in ALL patients, as shown in the UK studies, especially UKALL 2003: <p> 1. The predominant form is growth-spurt rated, occurs primarily when patients receive the offending steroid during the onset, or within a few years, of puberty. 1a. Girls are most vulnerable at the age of 12 to 14. 1b. Boys are most vulnerable at the age of 13 to 16, and are more vulnerable than girls, and more vulnerable than at any other age. 1c. Over the age span, adolescent boys and girls are at the highest risk of AVN. <p> 2. The 2nd most common form occurs in young adults and has a different pathogenesis. <p> 3. The least most common form occurs in children and it too has a different pathogenesis.. <p> 4. Adolescent boys and girls are at similar risk of AVN, as are young men and women. <p> 5. Asparaginase in the BFM chemotherapy setting does not increase the incidence of AVN and may even be protective, at least in adolescents. <p> 6. Prevention of menstruation in adolescent females may also be protective. Oncofertility applications occasionally include ovarian suppression, and if used in the UK should be included in data collection. <p> Combining the UKALL 2003 results with others, 7. Glucocorticoids (especially dexamethasone) are, by far, the primary etiology . <p> 8. The roles of antifolates (methotrexate) and asparaginase in AVN pathogenesis are uncertain. <p> 9. If asparaginase contributes it may only occur when given simultaneously with steroid and decreases steroid clearance. If given separately, it may be protective. <p> 10. The role of methotrexate may be limited to the young adult and/or childhood forms, the latter in whom methotrexate is known to cause osteoporosis and bone fractures by itself. <p> Some of these consideration, of which little is covered in the background section, should be considered for review, discussion and planning implementation.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1

Reviewer Name: Dr Bhavna Padhye

Comment:

It is a well written protocol, easy to read and follow in general oncology clinic.

When completed it will add significantly to our current understanding of osteonecrosis as we lack prospective data on this complication (as most studies are retrospective)

Many thanks for your comment. We hope that this study will advance our understanding of this challenging condition, particularly due to the lack of prospective studies in this field.

Response to reviewer 2

Reviewer Name: Riitta Niinimäki

Many thanks for your comments.

I have responded to each comment in turn:

Comment 1:

According to earlier studies it is known that osteonecrosis in cancer patients can be located all over the skeleton, not just lower extremities but also for upper extremities. The location of ON should be added: "the main aim is to determine the incidence of symptomatic and asymptomatic osteonecrosis in lower extremities..." Also, it should be added to the limitations that only osteonecrosis of lower extremities will be examined.

This has been added in as suggested.

Comment 2:

Introduction

Age as a risk factor has been described well with appropriate references. Other risk factors (sex and ethnicity) have been mentioned without references. High BMI has not been mentioned. Please, revise the clinical risk factors and add the references.

The chapter describing radiological classification is without references. Please, specify the classifications and add references.

The introduction has been amended with added detail and references

Comment 3:

Methods and analysis

MRI imaging

Please describe how osteonecrosis is defined radiologically.

A radiological definition for ON has been added in.

Comment 4:

Data analysis plan

"The grade of osteonecrosis will be assessed using a modified scoring system by reference using a study radiology proforma". Please add reference or explain more specifically.

Could you specify, if patient will develop symptomatic ON in upper limb, how the patient will be managed if she or he did not have any lesions in the lower limbs? Pain score is including also upper limbs.

The scoring system has been added in, with description of the modifications of your scoring system.

I have added in that upper limbs will only be scanned by the local team as per their standard management, but we will have access to these results.

Response to reviewer 3

Reviewer Name: Archie Bleyer

Many thanks for your very helpful commentary.

This is a prospective clinical study designed specifically to understand timing of asymptomatic and symptomatic lesions of osteonecrosis in young people being treated on UKALL2011, and to gain greater understanding of the natural history of osteonecrosis. Whilst we welcome these extensive comments, to expand on all of these in more detail would move the paper into the territory of being a literature review, and not a methodology paper as intended. However, the introduction has now been significantly expanded, with comments incorporated as appropriate.

Comment 1:

The statistical analysis is not presented, with the entire statistical section a single line that describes where it the statistical analysis will be done. Before a study of this type should be initiated, the feasibility, number of patients required (power), data validity/veracity, etc. must be proactively considered.

The statistical analysis has now been discussed in more detail. We have discussed missing data, and the power calculation in more detail.

Comment 2: Many germane prior publications are not discussed or even cited

I have now significantly expanded the introductory section of the article to incorporate more results of previous studies.

Comment 3. a) There are 3 types of avascular necrosis (AVN) in ALL patients, as shown in the UK studies, especially UKALL 2003:

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1. The predominant form is growth-spurt rated, occurs primarily when patients receive the offending steroid during the onset, or within a few years, of puberty.

1a. Girls are most vulnerable at the age of 12 to 14.

1b. Boys are most vulnerable at the age of 13 to 16, and are more vulnerable than girls, and more vulnerable than at any other age.

1c. Over the age span, adolescent boys and girls are at the highest risk of AVN.

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2. The 2nd most common form occurs in young adults and has a different pathogenesis.

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3. The least most common form occurs in children and it too has a different pathogenesis..

<p>

4. Adolescent boys and girls are at similar risk of AVN, as are young men and women.

I have added some more into the introduction to cover this. As far as I am aware, although there are likely to be different pathological processes in different age ranges of patients with ALL who develop osteonecrosis, they are not yet conclusively elucidated.

Comment 3b) Asparaginase in the BFM chemotherapy setting does not increase the incidence of AVN and may even be protective, at least in adolescents.

I have added additional information in the introduction regarding asparaginase, although I was unable to locate the reference that referred specifically to the protective element in adolescents.

Combining the UKALL 2003 results with others, 7. Glucocorticoids (especially dexamethasone) are, by far, the primary etiology .

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8. The roles of antifolates (methotrexate) and asparaginase in AVN pathogenesis are uncertain.

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9. If asparaginase contributes it may only occur when given simultaneously with steroid and decreases steroid clearance. If given separately, it may be protective.

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10. The role of methotrexate may be limited to the young adult and/or childhood forms, the latter in whom methotrexate is known to cause osteoporosis and bone fractures by itself.

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Some of these consideration, of which little is covered in the background section, should be considered for review, discussion and planning implementation.

These statements have all been considered and incorporated as appropriate.

VERSION 2 – REVIEW

REVIEWER	Riitta Niinimäki Oulu University Hospital, Department of Paediatrics Finland
REVIEW RETURNED	01-Mar-2019

GENERAL COMMENTS	I am happy with the revised manuscript. Good luck!