MANAGEMENT AND OUTCOME OF OSTEONECROSIS OF FEMORAL HEAD IN SKELETALLY IMMATURE PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

Background: Osteonecrosis is a problem that can happen when children with acute lymphoblastic leukemia (ALL) are being treated. The aftereffects of osteonecrosis are one of the most serious long-term complications for children being treated for acute lymphoblastic leukemia. The goal of this study is to examine how often and why osteonecrosis worsens in young patients with leukemia. Specifically, the study will focus on the hip bone.Patients and Methods: This study looked at patients who had a bone condition called osteonecrosis of the femoral head. They were identified using MRI scans and their images were checked using an electronic system called PACS. We did not include patients who were lost to follow-up or who did not have regular MRI screenings. We also did not include patients who had ON but it was not caused by childhood acute lymphoblastic leukemia. Examples of other causes include lymphoma, trauma, infection, slipped capital femoral epiphysis, or Legg–Calve´–Perthes disease. We also excluded patients who had less than one year of follow-up after their treatment ended.

Results: 2000 people were found to have ALL and were taken to the hospital for their treatment. Out of all the patients we examined, we found that 98 of them have a condition called osteonecrosis of the femoral head. Out of the total number of people, 47 were females, which is 48% of the group, and 51 were males, which is 52% of the group.Conclusion: The treatment of osteonecrosis of the hip in all patients, especially deciding when surgery is needed, is difficult for orthopedic surgeons. Knowing the cause, signs and symptoms, and how to diagnose a disease are important for treating it. However, it is important to have a strong sense of suspicion, to detect any issues early on, and to closely monitor for any further development. These actions are crucial for effectively managing the situation.

Keywords: osteonecrosis ;femoral head : acute lymphoblastic leukemia

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INTRODUCTION

Leukemia is a type of cancer that affects the blood. It usually affects children, especially those who are younger than 10 years old. (1) In the past few decades, there have been big improvements in treating this disease. It used to be deadly, but now it can be cured in most cases. (2)(3) This advances in the treatment is associated many complications which may result from the disease itself or from its treatment medications.(4) One of these complication is osteonecrosis which affect about one third of the cases and most commonly affects weight bearing joints.(5) The femoral head (part of the thigh bone) is a common place for a condition called osteonecrosis. This condition can cause no symptoms or a range of symptoms, from mild pain during everyday tasks to severe pain, difficulty walking, and limited movement of the hip. In books and stories, the occurrence of osteonecrosis of the femoral head can range from 1% to 7%. This mostly happens because of the different types of studies done or the methods used to find osteonecrosis. (6)(7) There are several things that can increase the chances of getting osteonecrosis of the femoral head, like the patient's age, where the osteonecrosis is located, and how big it is. (8) There are different ways to treat a condition called osteonecrosis of the femoral head. The best treatment for each person depends on their age, risk of leukemia, how well they can move their hip, and where and how big the bone damage is. (9)(10) Previous research on osteonecrosis in children with acute lymphoblastic leukemia has mostly focused on

European and North American study groups. These studies mainly aimed to identify the factors that put children at risk of developing osteonecrosis, rather than studying how the condition progresses in the femoral head. [11][12] Finding risk factors would help in figuring out who is at risk for osteonecrosis of the femoral head and what can be done to prevent it from getting worse. So, the purpose of this study was to examine how often and why osteonecrosis of the femoral head gets worse in children with ALL at the Children Cancer Hospital Egypt 57357. We looked at information from 2000 patients who were diagnosed with ALL and went to the hospital for treatment. Patients with osteonecrosis were mostly identified by their symptoms. Imaging studies were then done to confirm the presence of osteonecrosis in all patients.

MATERIALS AND METHODS

We got permission from our review board and looked back at all the medical information we had on children with acute lymphoblastic leukemia who came to our hospital from 2008 to 2015. We looked at all the pictures (x-rays and MRIs) of people's hips with an experienced doctor to find and diagnose cases of a hip problem called osteonecrosis of the femoral head. The study included patients who had a bone condition in their hip called osteonecrosis of the femoral head. The doctors used MRI scans and looked at the images over time using a computer system called PACS. We did not include patients who did not continue with their medical check-ups or did not have regular MRI scans. We also did not include patients who developed optic nerve damage from another condition besides childhood acute lymphoblastic leukemia, such as lymphoma, injury, infection, problems with the hip bones, or Legg–Calve´–Perthes disease. Additionally, we did not include patients who were not followed up for at least one year after their treatment ended. We found a condition called osteonecrosis in the hip bone to see how often it occurs. We collected information about different things like the age and sex of the patient, whether the problem affected one side or both sides of the body, the risk of leukemia, when the problem started in relation to when treatment began, and the type of treatment received for osteoencrosis (either removing part of the bone or using other methods). We also looked at how these things affected the progression of the disease, using a system called Stulberg classification. [13] Doctors looked at the patients using x-ray and MRI scans to find out where the problem was in their body. They also checked if the problem was on one side or both sides, and how big it was compared to the rest of a bone in their hip. They used certain classifications to see how the problem affected the surface of the bone and if it would get worse over time. The radiological assessment of osteonecrosis of the femoral head was categorized using the Steinberg classification [14] and lateral pillar classification [15] at first presentation and according to Stulberg classification at final follow up in all patients to detect disease progression. The Stulberg classification rates hip shape in different grades. Grade 1 is a normal round hip joint. Grade 2 is a round hip joint but with a short neck or steep socket. Grade 3 is an oval-shaped hip joint. Grade 4 is a non-round hip joint that fits well with the socket. Grade 5 is a non-round hip joint that doesn't fit well with the socket. In our study, we thought that grades 1 and 2 were good results, grade 3 was okay, and grades 4 and 5 were not so good.

Statistical Analysis

We used a program called The Statistical Package for the Social Sciences (SPSS), version 25, made by IBM Corp in Armonk, NY, USA, to analyze the data. The information included averages, confidence intervals, middle values, minimum and maximum values, percentages, and actual numbers. We checked if the data follows a normal pattern by using the Shapiro-Wilk and Kolmogorov-Smirnov tests. To figure out how different factors affect the final Stulberg, we used a mixed model that takes into account all the patient IDs as well as the risk factors such as age, sex, bilateral affection, site, side, LPC, bone density, timing, core decompression, and necrosis reaching the AS. We considered a p-value less than 0. 05 as statistically significant. [16]

RESULTS

After reviewing the clinical database, 2000 patients were diagnosed with ALL and admitted to the hospital to receive their treatment. Among those patients, we diagnosed 98 patients with osteonecrosis of femoral head. Of which 47 were females (48%) and 51 were males (52%). Fifty-eight patients (59.2%) had bilateral involvement and 40 patients (40.8%) had unilateral involvement. Of the unilateral cases, 20 (50%) patients had an involvement in the right femoral head and 20 (50%) in the left femoral head. Mean age at diagnosis was 12.27 years (95%CI 11.47- 13.05). Most of the patients (73 patients, 74.5%) were on the standard risk protocol, 14 patients (14.3%) were on the high risk protocol and 11 patients (11.2%) were on the low risk protocol. The incidence of osteonecrosis of femoral head was 4.9% among all patients in selected study period. The median age at diagnosis was 13 years (range 3-18).and male to female ratio was approximately 1: 1. The mean time for occurrence of osteonecrosis of femoral head in relation to diagnosis and starting of treatment was 17 months (95%CI 15.2-18.8), median 13 (range 1-54) (**table 1**). We analyzed all risk factors and their relation to disease progression according to Stulberg classification. There were 98 patients with osteonecrosis of femoral head and of them 58 cases had bilateral affection and there were difference

between both sides in relation to some risk factors so, in those patients these risk factors will be analyzed per joint and number of joints that were be analyzed was 156 joints. According to age of the patient at diagnosis of osteonecrosis of femoral head (per patient), We divided patients into two groups, first group below age of 10 years (10 years or less) and second group above age of 10 years, Increase the age was not significantly associated with progression of osteonecrosis (P value 0.087) (**table 2**). Also, sex (per patient) was not significantly associated with progression of osteonecrosis (P value 0.6). While, there was a significant correlation between laterality and disease progression. Patients with bilateral involvement are more likely to have a poorer outcome (P value 0.006). To analyze effect of osteoporosis (per patient) on osteonecrosis progression, we divided patients into three grades according to DEXA scan and bone quality on x-ray, grade 1 is normal(Z-scores is more than -1), grade 2 is osteopenic (Z-scores between -1 and -2.5) and grade 3 is osteoporotic (Z-scores less than -2.5).Forty-four patients (44.9%) were osteopenic, 21 patients (23.7%) were osteoporotic and 33 patients (32.7%) were normal. Bone density was not associated with osteonecrosis progression (P value 0.06). The mean time for occurrence of osteonecrosis was 17 month (95%CI 15.2-18.8), median 13 (range 1-54). We divided cases into two groups (per patient) according to timing of occurrence of osteonecrosis in relation to start of ALL treatment, first group with early occurrence of osteonecrosis in relation to treatment (less than two years) and second group with late timing of occurrence (more than two years). There was significant relationship between timing of osteonecrosis occurrence in relation to ALL diagnosis and start of treatment and disease progression with high incidence of disease progression according to Stulberg classification in the first group (less than two years) (P value 0.007). Size of osteonecrosis of femoral head was classified to three sub types **(table 3)**, (A less than 15%, B 15-30% and C more than 30 %) in coronal view of MRI according to classification of Steinberg classification (per joint) Eighty six joints (55.1%) had a size less than 15%, 16 (10.3%) had size between 15-30% and 54 (34.6%) had a size more than 30%.There was a significant relation between size of osteonecrosis and disease progression where joints having a small size (class A) of necrosis are less likely to have a poor outcome with disease progression (P-value 0.016). We divided the femoral head to three equal parts medial, lateral and intermediate and if the necrosis involved the three parts, it was considered diffuse. Having a diffuse site affection followed by lateral site affection (weight bearing area) were significantly associated with poorer outcome (higher Stulberg) (P-value 0.001) **(table 4)**. We classified osteonecrosis of femoral head to two subtypes in the coronal view of MRI, type (1) is firmly related to articular surface and type (2) is away from articular surface and separated from articular joint by normal subchondral bone **(table 5)**. There was a relation to articular surface in 126 joints (80.8%) and no relation in 30 joints (19. 2%).Patients with necrosis reaching the articular surface were significantly more likely to have a poorer outcome and higher Stulberg (P value 0.02). We revised collapse of lateral pillar according to lateral pillar (LPC) classification and its impact to progression of the disease (per joint) **(table 6)**. Hundred and thirty five joints (86.5%) had graded A, 17(10.9%) had graded B and 4 (2.6%) joints had graded C, Patients with LPC (Grade A) are significantly less likely to develop poorer outcome (P-value 0.012) so, lateral pillar classification has significant value for predicting the prognosis of AVN estimated using the Stulberg classification. There was no significant relation between risk stratification (per patient) and osteonecrosis progression. Most of the patients (73 patients, 74.5%) were on the standard risk protocol, 14 patients (14.3%) were on the high risk protocol and 11 patients (11.2%) were on the low risk protocol .According to our hospital's protocol for management of ALL the standard risk and high risk leukemia have the same strategies of treatment. According to our protocol for management of cases with osteonecrosis of femoral head, 97 joints were treated by core decompression and 59 joints were treated by conservative means in form of restriction of weight bearing and physical therapy and by comparing the two methods and their effect on limitation of progression of osteonecrosis **(table 7)**, there was no difference between the two methods with no significance on improving the outcome with P value (P=0.066).

MULTIVARIATE ANALYSIS:

When the variables tested in univariate analysis above were tested in multivariate analysis, being bilateral (P-values 0.006), having diffuse involvement (P-values 0.008) or lateral involvement (P-values 0.015) and having a size C necrosis (P-values 0.016) of femoral head were significantly associated with progression of osteonecrosis.

Table (1): Table illustrating incidence of osteonecrosis in relation to some risk factors:

		Count	%
side	**bilateral**	58	49.0%
	unilateral	40	41.0%
age	**<10 years**	29	29.6%
	>10 years	69	70.4%
Sex	**M**	51	52.0%
	F	47	48.0%
size of osteonecrosis	**A**	81	51.9%
	B	18	11.5%
	C	57	36.6%
osteoporosis	**normal**	33	33.6%
	osteopenia	44	44.9%
	osteoporotic	21	21.4%
LPC	**A**	135	86.5%
	B	17	10.9%
	C	4	2.6%
Relation To AS	**Yes**	126	80.8%
	No	30	19.2%

Table (2): Table illustrating relation between age and final Stulberg classification:

			Final stulberg					
			1	2	3	4	5	Total
Age	At Less than 10Ys	Count	20	4	3	0	2	29
		%	69%	14%	10%		7%	100%
	More than 10Ys	Count	37	5	6	12	9	69
		%	54%	7%	9%	17%	13%	100%

Table (3): Table illustrating relation between size of osteonecrosis and final Stulberg classification:

			Final stulberg					
			1	2	3	4	5	Total
Size	A	Count	59	2	5	8	7	81
		%	73%	2.5%	6%	10%	8.5%	100%
	B	Count	8	3	4	2	1	18

		%	44%	17%	22%	11%	6%	100%
	C	Count	13	9	10	14	11	57
		%	23%	16%	18%	24%	19%	100%

Table (4): Table illustrating relation of site of osteonecrosis and final Stulberg classification:

			Final Stulberg					**Total**
			1	**2**	**3**	**4**	**5**	
Site	Diffuse	Count	7	6	9	18	11	51
		% within site2	13.7%	11.8%	17.6%	35.3%	21.6%	100.0%
	Lateral	Count	14	1	5	5	3	28
		% within site2	50.0%	3.6%	17.9%	17.9%	10.7%	100.0%
	Medial	Count	15	0	0	0	1	16
		% within site2	93.8%	0.0%	0.0%	0.0%	6.3%	100.0%
	Middle	Count	32	2	3	0	2	39
		% within site2	82.1%	5.1%	7.7%	0.0%	5.1%	100.0%
	Two parts affected	Count	16	3	2	0	1	22
		% within site2	72.7%	13.6%	9.1%	0.0%	4.5%	100.0%
Total		Count	84	12	19	23	18	156
		% within site2	53.8%	7.7%	12.2%	14.7%	11.5%	100.0%

Table (5): Table illustrating relation between relation of osteonecrosis to articular surafce and final Stulberg classification:

			Final stulberg					
			1	2	3	4	5	Total
Relation To AS	No	Count	26	0	0	2	2	30
		% within Relation To AS	86.7%	0.0%	0.0%	6.7%	6.7%	100.0%
	Yes	Count	58	12	19	21	16	126
		% within Relation To AS	46.0%	9.5%	15.1%	16.7%	12.7%	100.0%
Total		Count	84	12	19	23	18	156
		% within Relation To AS	53.8%	7.7%	12.2%	14.7%	11.5%	100.0%

Table (5): Table illustrating relation between collapse of lateral pillar and final Stulberg classification:

			Final stulberg					
			1	2	3	4	5	Total
LPC	A	Count	84	10	13	19	9	135
		% within LPC	62.2%	7.4%	9.6%	14.1%	6.7%	100.0%
	B	Count	0	2	6	3	6	17
		% within LPC	0.0%	11.8%	35.3%	17.6%	35.3%	100.0%

C	Count	0	0	0	1	3	4
	% within LPC	0.0%	0.0%	0.0%	25.0%	75.0%	100.0%
Total	Count	84	12	19	23	18	156
	% within LPC	53.8%	7.7%	12.2%	14.7%	11.5%	100.0%

Table (3): Relation of management of osteonecrosis by core decompression (yes) or conservative means (no) and final Stulberg classification.

			Final Stulberg					Total
			1	2	3	4	5	
Core decompression	No	Count	63	6	7	7	14	97
		% within Core decompression	64.9%	6.2%	7.2%	7.2%	14.4%	100.0%
	yes	Count	21	6	12	16	4	59
		% within Core decompression	35.6%	10.2%	20.3%	27.1%	6.8%	100.0%
Total		Count	84	12	19	23	18	156
		% within Core decompression	53.8%	7.7%	12.2%	14.7%	11.5%	100.0%

DISCUSSION

Avascular necrosis is a serious problem that can happen if you have leukemia or lymphoma and are treated with chemotherapy or high doses of steroids. It can cause a lot of trouble and make it hard for you to do things. [3][17] Other things like not being able to move or having cancer can also cause avascular necrosis to happen. [4] Our estimate was 4. 9%, which is nearly the same as the Patel B et al's report of 4% in 1053 patients,[18] higher than the study from Greece that found a cumulative incidence of 2.5% in 276 patients[19] and A study from Italy discovered that 3691 patients had a total infection rate of 2. 7% [20] and lower than the study described by Bhavna Padhye et al with incidence of 7%.[21] In some other cohorts, reported incidences have been variable, ranging from 7.1 to 14%.[22][23] In our study, we found that the age and sex of the participants did not have a significant impact on disease progression. However, other studies have shown that age is an important risk factor for disease progression, as reported by Relling et al, Burger et al, Lackner et al, Kadan-Lottick et al, and Vora et al. [4][24] [25][26][27] We couldn't find a clear reason for this difference, even though our group was very big. In simpler terms, sex did not have a big impact in this study, just like many other studies.,[4][21] although, Mattano et al, reported an increased incidence of osteonecrosis in females. [22] Moreover male to female ratio in our study was 1:1 which is similar to that described by Rosanna Parasole et al. [20] In our study, the mean time for occurrence of osteonecrosis from date of diagnosis and start of treatment was 17 month which is also comparable with many existing studies that reported a 14-27 month median time interval from leukemia diagnosis to ON occurrence.[28][24] Also, Bhavna Padhye et al and Kaste. S et al reported that the mean time from diagnosis of ALL to that of osteonecrosis development was between 1 and 2 years.[9][29][21][30] Also, we reported that early occurrence of osteonecrosis of femoral head (within two years) in relation to diagnosis of ALL and start of treatment is significantly associated with necrosis progression in comparison to late timing of osteonecrosis occurrence. The incidence of osteonecrosis occurrence in relation to diagnosis of ALL in our study was mainly in the first two years (80 cases of 98) which is similar to majority of other studies and this may be theoretically attributed to glucocorticoid and chemotherapy exposure during treatment of leukemia.[4][5] On the other hand, there are several case reports on osteonecrosis detected on diagnosis before the start of any treatment. [31] Regarding site, size of osteonecrosis and its relation to articular surface in our study, all had a significant relation to osteonecrosis progression (diffuse or lateral site of osteonecrosis, related to articular surface and large size of osteonecrosis more than 30 % of whole size of femoral head) which is similar to the study of Evguenia J. Karimova et al, who reported that large femoral head size lesion had a significant relation to progression of osteonecrosis. [9] Also Steinberg et al [32] showed that when the necrotic area was small, and particularly when it was located in the non-

weight bearing area of the femoral head and the patient was clinically asymptomatic, avascular necrosis of the femoral head can have a good course. In contrast, there were reports that avascular necrosis of the femoral head is progressive regardless of the size and site of the lesion as that reported by Beguin et al.[33] Regarding bone density and quality of the bone in our study, osteoporosis or decreased bone density was not a significant risk factor for disease progression. There are many risk factors for development of decreased bone mineral density as Osteotoxic chemotherapy, steroid exposure, poor nutrition, low vitamin D, and poor muscle mass that contribute to the development or worsening of bone pathology.[34] While Karimova EJ et al, reported that there is an overlap exists between risk factors for low bone mineral density and osteonecrosis in pediatric patients with ALL.[9][35] Some authors recommended use of bisphosphonates for treatment of low mineral density and bone fragility during management of ALL [36] while, others recommended use of bisphosphonates for management of osteonecrosis based on its role for inhibition of osteoclastic activity which inhibit resorpation of osteoencrotic fragment and this give chance for revascularization and avoid subchondral collapse and flattening of head following resorpation of osteonecrotic fragment.[37][38][39] Regarding the risk stratification of acute lymphoblastic leukemia in our study there was no significant relation between risk stratification and osteonecrosis progression which is similar to what Rosanna Parasole et al reported that there was no statistical difference regarding risk group stratification. [20] Also, Bhavna, Padhye et al reported that there was no relation between risk stratification and osteonecrosis incidence and progression and incidence of osteonecrosis regarding the risk in his study was 3.4% patients in SR, 7.5% in LR, 13.8% in VHR group and no patients in HR group.[37] Regarding management by core decompression, our study stated that management by core decompression didn't prevent or limit progression of osteonecrois. Also, Evguenia J. Karimova et al, did thirty five core decompressions in patients (pediatrics and young adults) with no effect on prevention or delay of joint surface collapse or arthroplasty.[9] Moreover, Plenk H et al reported that the repair after core decompression alone is usually incomplete and is only likely to delay, but not prevent the progression of joint destruction,[40] while Schneider W et al and Rajagopal M et al reported that in early stage of femoral head necrosis, core decompression might lead to significant postoperative pain reduction. [41][42] Moreover in a retrospective systematic review done by Michael D et al showed that previous core decompression was not associated with decreased incidence of collapse and arthroplasty. [43] In contrast meta analysis by Castro and Barrack demonstrated better results with core decompression compared with non operative management. [44] Most of the studies of treatment for ONFH have been done on the adult population and treatment strategies have been adopted into the pediatric group. So, bone marrow aspirants have been advocated as an exciting new method for delivering mesenchymal stem cells to the necrotic area after core decompression to encourage osteogenesis. However, for the patients undergoing active treatment, there is a theoretical concern for harvesting and transfer of malignant cells from an occult source in the bone marrow so; bone aspirant with core decompression should only be considered for patients in remission or who are off therapy. [45] However Sculley and Coworkers, have advocated the use of vascularized fibular grafts to the core decompression to provide some structural support. They demonstrated high success rates in patients with early stage of the necrosis, [46] but there are some limitations to this technique as the procedure is highly demanding, donor site morbidity and postoperative complication that may lead to delay of continuation of leukemia treatment. [47] On the other hand, some of our cases were treated conservatively by restriction of full weight bearing, physical exercises and avoidance of vigorous activity and there was no statistical significance that conservative means prevented or delayed progression of osteonecrosis of femoral head. In contrast some authors recommended use of non-operative treatment in the form of restriction of weight bearing, bracing, physical therapy and medical treatment as a treatment modality for osteonecrosis of femoral head. [48] While a meta-analysis of non-operative treatment of twenty-one studies involving 819 hips revealed that with restricted weight bearing modality, only 22.7% of the hips were satisfactory clinically (range 0 to 44%) and seventy-six per cent of the hips (range 44 to 100%) required hip arthroplasty or a salvage procedure.[49]

CONCLUSION

The management of the osteonecrosis of femoral head in ALL patients especially in determining the indications and timing of surgical intervention remains a challenge to the orthopedic surgeon. Knowledge of the etiology, pathology, presentation (symptomatic or asymptomatic) and diagnosis are keys to treatment. But, high suspicion level, early detection and closed follow up to detect any progression are instrumental in successful management. So, we advocate closed follow ups in patients with the following criteria, children near skeletal maturity, bilateral osteonecrosis, large osteonecrosis which is more than 30% of whole volume of femoral head, osteonecrosis related to

articular surface and which is located in weight bearing area of femoral head.

REFERENCES

1-Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Möricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115(16):3206-14.

2-Friedmann AM, Weinstein HJ. The role of prognostic features in the treatment of childhood acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009;23(5):1033-42.

3-Girald, P. et al. Symptomatic osteonecrosis in childhood leukemia survivors: prevalence, risk factors and impact on quality of life in adulthood. Haematologica 2013; 98, 1089–1097.

4-Burger, B. et al. Osteonecrosis: a treatment related toxicity in children with acute lymphoblastic leukemia (ALL)-experiences from trials ALL-BFM 95.Pediatr. Blood. Cancer 44, 220–225 (2005).

5-Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. Haematologica. 2003;88:747–753.

6-Steinberg ME, Mont MA. Osteonecrosis. In: Chapman MW, ed. Chapman's Orthopaedic Surgery. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:3263-3308.

7-Nakamura T, Matsumoto T, Nishino M, Tomita K, Kadoya M: Early magnetic resonance imaging and histologic findings in a model of femoral head necrosis. Clin Orthop 1997;334:68-72.

8-Kalpit N. Shah1, Jennifer Racine, Lynne C. Jones2, Roy K. Aaron. Pathophysiology and risk factors for osteonecrosis. Curr Rev Musculoskelet Med 2015; 8:201–209.

9-Karimova, E.J., Rai, S.N., Howard, S.C., Neel, M., Britton, L., Pui, C.H. & Kaste, S.C. Femoral head osteonecrosis in pediatric and young adult patients with leukemia or lymphoma. Journal of Clinical Oncology.2007; 25, 1525–1531.

10-te Winkel ML, Pieters R, Wind E-JD, Bessems JHJM and van den Heuvel-Eibrink MM: Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia. Haematologica 99: 430-436, 2014. PMID: 24598854, DOI: 10.3324/haematol.2013.095562.

11- Pauline Girard, Pascal Auquier, Vincent Barlogis. Symptomatic osteonecrosis in childhood leukemia survivors: prevalence, risk factors and impact on quality of life in adulthood. Haematologica 2013;98. doi:10.3324/haematol.2012.081265.

12-Akinyoola AL, Adediran IA, Asaleye CM (2007) Avascular necrosis of the femoral head in sickle cell disease in Nigeria: a retrospective study. Niger Postgrad Med J 14(3):217–220.

13-Stulberg SD et al.:The natural history of legg-clave-perthes' disease.Bone Joint Surg Am. 1981,63(7):1095-1108.

14-Garino JP, Steinberg ME:Total hip arthroplasty in patients with avascular necrosis of the femoral head: A 2-to10-year follow-up. Clin Orthop 1997; 334:108-115.

15-Herring JA et al.:The lateral pillar classification of leggcalve perthes disease. Pediatric Orthop 1992,12:143-50.

16-Gray RJ.A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988; 16:1141–54.15. Fine JP, Gray RJ. A proportional.

17- 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; 29:4143–4150.

18-PatelB, Richards SM, Rowe JM, Goldstone AH, Fielding AK.High incidence of avascular necrosis in adolescents with acute lymphoblasticleukemia: a UKALL XII analysis. Leukemia. 2008;22(2):308-12.

19- Tragiannidis A, Athanassiadou F, Papageorgiou T, Petsatodis G, Sidi V, Kolouskas D.Osteonecrosis in children with acute lymphoblastic leukemia:a 10 year study from Northern Greece. Pediatr Blood Cancer. 2007;49(5):764.

20. Rosanna P, Maria V, Daniela S.Correspondence: Osteonecrosis in childhood acute lymphoblastic leukemia: a retrospective cohort study of the Italian Association of Pediatric Haemato-Oncology (AIEOP). Blood Cancer Journal.2018; 8:115

21. Bhavna P,Luciano D, David L.: Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). Caner Med.2016; 5(5): 960–967.

22. Mattano LA Jr, Sather HN, Trigg ME, Nachman JB.Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the children's cancer group. J Clin Oncol. 2000; 18(18):3262-72.

23. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al.Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360(26):2730-41.

24. Vora, A., Wade, R., Mitchell, C., Goulden, N. & Richards, S.:Incidence and outcome of

osteonecrosis in children and young adults with acute lymphoblastic leukemiatreated on a dexamethasone containing protocol: results of the medical research council UK Trial ALL 2003. Blood (ASH Annual Meeting Abstracts)2008; 112, 910.

25. Relling, M.V., Yang, W., Das, S., Cook, E.H., Rosner, G.L., Neel, M., Howard, S., Ribeiro, R., Sandlund, J.T., Pui, C.H. & Kaste, S.C.Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. Journal of Clinical Oncology.2004;22, 3930–3936.

26-Ajay Vora.Management of osteonecrosis in children and young adults with acute lymphoblastic leukemia. British Journal of Haematology. 2011;155, 549–560.

27- Lackner, H., Benesch, M., Moser, A., Smolle-Juttner, F.,Linhart, W., Raith, J. & Urban, C.Aseptic osteonecrosis in children and adolescents treated for hemato-oncologic diseases: a 13-year longitudinal observational study. Journal ofPediatric Hematology andoncology.2005; 27, 259–263.

28-Boettcher WG, Bonfi glio M, Smith K.Nontraumatic necrosis of the femoral head, II: experiences in treatment. J Bone Joint Surg Am. 1970; 52(2):322-9.

29-Madadi F, Shamsian BS, Alavi S, Madadi F, Eajazi A, Aslani A.:Avascular necrosis of the femoral head in children with acute lymphoblastic leukemia: a 4-to 9-year follow up study. Orthopedics. 2011;34:593-597.

30-Kaste, S. 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, 610–615.

31-Niebrugge DJ, Benjamin DR.Bone marrow necrosis preceding acute lymphoblastic leukemia in childhood. Cancer. 1983;52(11):2162–2164.

32-Steinberg ME, Bands RE, Parry S, Hoffman E, Chan T, Hartman KM.Does lesion size affect the outcome in avascular necrosis? Clin Orthop Relat Res. 1999; (367):262-271.

33-Beguin A, Bertrand Y, Ourcival S, Foray P, Manel AM, Philippe N.Aseptic femur head osteonecrosis during treatment of acute lymphoblasticleukemia in the child [in French]. Arch Pediatr. 1999; 6(9):971-974.

34-Sogol MandJacqueline H.Bone Morbidity in Childhood Leukemia: Epidemiology, Mechanisms, Diagnosis, and Treatment. Curr Osteoporos Rep. 2014; 12(3): 300–312.

35-Crock H.A revision of the anatomy of the arteries supplying the upper end of the human femur. J Anat. 1965;99:77–88.

36-Lethaby C, Wiernikowski J, Sala A, et al.Bisphosphonate therapy for reduced bone mineral density during treatment of acute lymphoblastic leukemia in childhood and adolescence: a report of preliminary experience.J Pediatr Hematol Oncol. 2007;29(9):613–616.

37. Padhye B, Dalla-Pozza L, Little DG, et al:Use of zoledronic acid for treatment of chemotherapy related osteonecrosis in children and adolescents: A retrospective analysis. Pediatr Blood Cancer. 2013; 60:1539-1545.

38. Yuan HF, Guo CA, Yan ZQ:The use of bisphosphonate in the treatment of osteonecrosis of the femoral head: A meta-analysis of randomized control trials. Osteoporos Int. 2016; 27:295-299.

39. Sanjay Agarwala Shripad D. Banavali Mayank Vijayvargiya.Bisphosphonate Combination Therapy in the Management of Postchemotherapy Avascular Necrosis of the Femoral Head in Adolescents and Young Adults: A Retrospective Study from India. J Glob Oncol. 2018;154.16.60.79.

40-Plenk H Jr, Hofmann S, Breitenseher M, Urban M.Pathomorphological aspects and repair mechanisms of femur head necrosis.Orthopade. 2000;29(5):389-402.

41-Rajagopal M, Balch Samora J, Ellis TJ.Efficacy of core decompression as treatment for osteonecrosis of the hip: a systematic review.Hip Int. 2012;22(5):489-493.

42. Schneider W, Breitenseher M, Engel A, Knahr K, Plenk H Jr, Hofmann S.The value of core decompression in treatment of femur head necrosis.Orthopade. 2000;29(5):420-429.

43-Michael D.N, and Evguenia J.K.Osteonecrosis of the Femoral Head in Pediatric Cancer Patients. Semin Arthro. 2007; 18:203-210.

44-Castro FP Jr, Barrack RL:Core decompression and conservative treatment for avascular necrosis of the femoral head: A meta-analysis. Am J Orthop. 2000; 29:187-194.

45Gangji V, Toungouz M, Hauzeur JP:Stem cell therapy for osteonecrosis of the femoral head. Expert Opin Biol Ther. 2005 5:437-442.

46. Scully SP, Aaron RK, Urbaniak JR:Survival analysis of hips treated with core decompression or vascularized fibular grafting because of avascular necrosis. J Bone Joint Surg Am. 1998; 80:1270-1275.

47-Sotereanos DG, Plakseychuk AY, Rubash HE:Free vascularized fibula grafting for the treatment of osteonecrosis of the femoral head. Clin Orthop 1997;344:243-256.

48-Cheng EY, Thongtrangan I, Laorr A, Saleh KJ.Spontaneous resolution of osteonecrosis of the femoral head.J Bone Joint Surg Am.2004; 86:2594–9.

49- Shin-Yoon Kim and Tae-Ho Kim.Genome-wide association scansfor idiopathic osteonecrosis of

femoral head in Korean population. Mol Med Rep 2017; 15(2): 750–758.